A Chiron Approach Towards Synthesis of Naturally Occurring Lactones *via* Ring Closing Metathesis and Development of Methodologies Under Solvent Free and Triphasic Conditions

A Thesis Submitted
in Partial Fulfillment of the Requirements
for the Degree of

DOCTOR OF PHILOSOPHY

by

R. Vijaya Anand

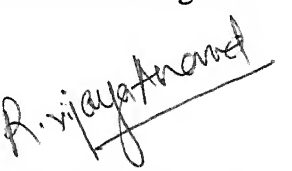
to the

DEPARTMENT OF CHEMISTRY
INDIAN INSTITUTE OF TECHNOLOGY,
KANPUR, INDIA
February, 2003

STATEMENT

I hereby declare that the matter manifested in this thesis, "**A Chiron Approach Towards Synthesis of Naturally Occurring Lactones *via* Ring Closing Metathesis and Development of Methodologies Under Solvent Free and Triphasic Conditions**" is the result of research carried out by me in the Department of Chemistry, Indian Institute of Technology, Kanpur, India under the supervision of Prof. Vinod K. Singh.

In keeping with general practice of reporting scientific observations, due acknowledgements have been made wherever the work described is based on the findings of other investigators.



IIT Kanpur

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CERTIFICATE

It is certified that the work encapsulated in the thesis entitled, "**A Chiron Approach Towards Synthesis of Naturally Occurring Lactones *via* Ring Closing Metathesis and Development of Methodologies Under Solvent Free and Triphasic Conditions**" by R. Vijaya Anand has been carried out under my supervision and this work has not been submitted elsewhere for a degree.

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Certificate of Course Work

This is to certify that **R. Vijaya Anand** has satisfactorily completed all the courses required for the Ph.D. degree. The courses include:

CHM 602	Advanced Organic Chemistry II
CHM 611	Physical Organic Chemistry
CHM 631	Applications of Modern Instrumental Methods
CHM 664	Modern Physical Methods in Chemistry
CHM 612	Frontiers in Organic Chemistry
CHM 668	Advanced Main Group Chemistry
CHM 800	General Seminar
CHM 801	Graduate Seminar
CHM 900	Postgraduate Research

R. Vijaya Anand was admitted to the candidacy of the Ph.D. degree in September 1998 after he successfully completed the written and oral qualifying examinations.

Prof. S. Sarkar
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for Prof. K. Srihari
Convenor, DPGC
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... Dedicated to my parents

and teachers

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Vijay

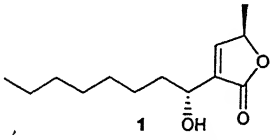
Synopsis

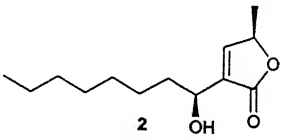
The thesis entitled "**A Chiron Approach Towards Synthesis of Naturally Occurring Lactones *via* Ring Closing Metathesis and Development of Methodologies Under Solvent Free and Triphasic Conditions**" is mainly divided into two parts, namely part A and part B. Part A deals with an approach towards the synthesis of naturally occurring lactones via ring closing metathesis and part B deals with the development of methodologies under solvent free and triphasic conditions.

Part A is sub divided into 3 chapters. Chapter 1 is a comprehensive review on ring-closing metathesis (RCM), which has recently emerged as a powerful tool for the formation of a variety of ring systems. The application of RCM in organic synthesis and the recent developments in catalyst design are discussed in this chapter.

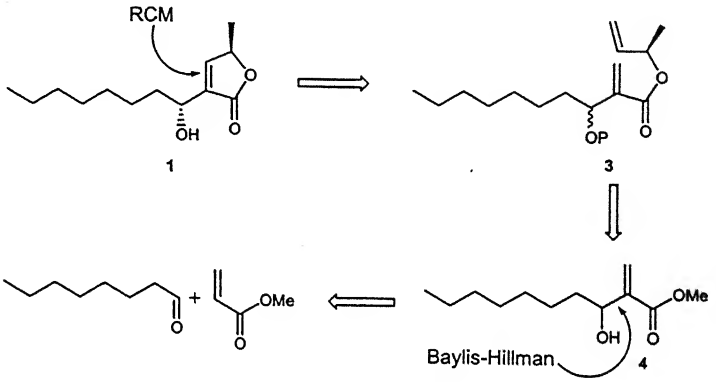
In chapter 2, we have described the total synthesis of (-)-acaterin **1** and its diastereomer **2** using ring closing metathesis as a key step. We have also attempted the synthesis of (*S*)-fugomycin (**5**) by applying ring closing enyne metathesis.

(-)-Acaterin **1**, isolated from *Pseodomonas sp.* A92, is an inhibitor of Acyl CoA: Cholesterol Acyl Transferase (ACAT) and is expected to be effective for treatment of atherosclerosis and hypercholesterolemia.





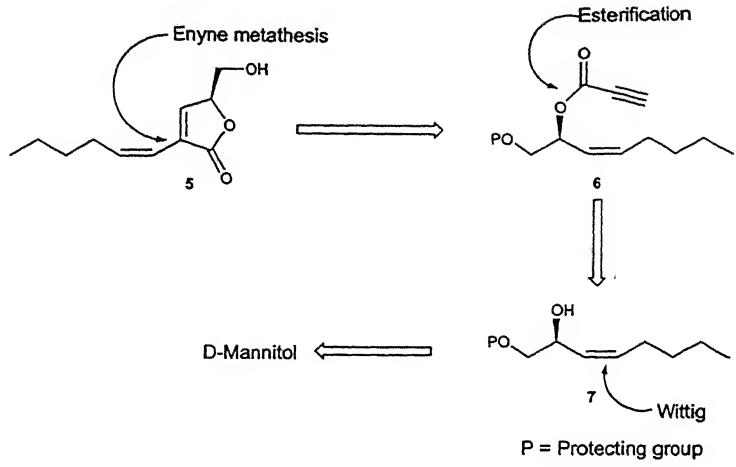
The starting material chosen for the synthesis of acaterin was a Baylis-Hillman adduct **4** derived from caprylic aldehyde and methyl acrylate (Scheme 1). The adduct **4** was transformed to the diene ester **3** in 3 steps. The five membered ring of (-)-acaterin was constructed using RCM strategy.



Scheme 1. Retrosynthetic analysis of (-)-acaterin.

(*S*)-Fugomycin **5** was isolated from *Pseudomonas aureofaciens* and was found to have remarkable antifungal activity. The starting material used for the synthesis of (*S*)-fugomycin **5** was commercially available and inexpensive D-mannitol. The mono protected diol **7** was synthesized from D-mannitol in 5 steps. But the attempt to convert the alcohol **7** to its corresponding propiolate ester **6** under various reported esterification conditions failed. Further

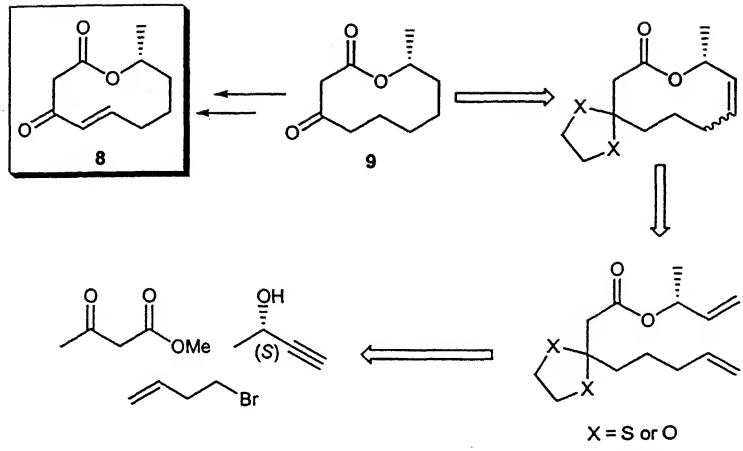
investigation to synthesize the enyne (**6**) from other starting materials is currently under progress.



Scheme 2. Retrosynthetic analysis of (*S*)-fugomycin

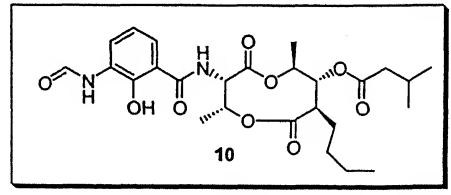
Chapter 3 involves a formal synthesis of (+)-diplodialide A **8** and the approach towards synthesis of macrolide core of Antimycin A_3 **10** using ring closing metathesis strategy.

Diplodialide A **8** was isolated from a Fungus *Diplodia pinea* and is a steroid hydroxylase inhibitor. The formal synthesis of (+)-diplodialide A **8** was achieved by using methyl acetoacetate as a starting material and we have used RCM strategy for the construction of the macrocyclic β-keto lactone ring **9** (Scheme 3). Since the synthesis of diplodialide A **8** from the β-keto lactone **9** is known in the literature, we have achieved the formal synthesis of (+)-diplodialide A **8**.

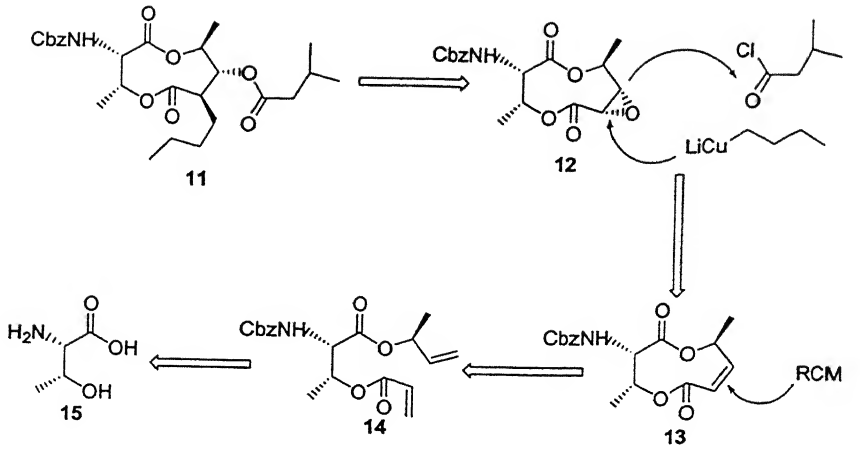


Scheme 3. Retrosynthetic analysis of (+)-diplodialide A.

In chapter 3, we have also described a shortest approach towards to the synthesis of the macrolide core of antimycin A_3. Antimycin A_3 **10** is an antibiotic and antifungal agent isolated from *streptomyces* species and is a nine membered dilactone.

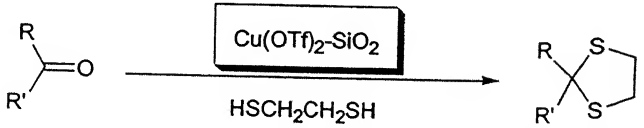


The Retrosynthetic analysis of the macrolide core of antimycin A_3 is given in Scheme 4. We used *L*-threonine **15** as a starting material for the synthesis of antimycin A_3. The macrocyclization of **14** was performed using RCM strategy. In the macrocyclization step we got the cyclized product as a 1:1 mixture of *cis* and *trans* isomers (**13**). Only the *cis* isomer can be converted to the natural antimycin A_3. Further investigation to improve *Z/E* ratio is currently under progress.



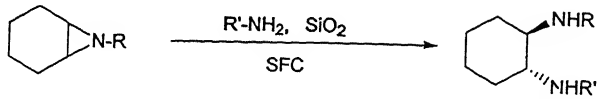
Scheme 4. Retrosynthetic analysis of Antimycin A_3.

Part B is sub divided into 2 chapters. Chapter 1 deals with solvent free reactions. During the synthesis of (-)-diplodialide we observed that $Cu(OTf)_2$ efficiently catalysed the conversion of a ketone intermediate to its corresponding thio ketal. This result prompted us to investigate the thoacetalization reaction in detail. Since solvent free reactions have many advantages over solution phase chemistry, we explored this methodology under solvent free conditions using $Cu(OTf)_2$ adsorbed on silica gel as a catalyst.

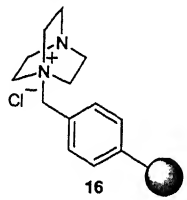


We further studied the solvent free aziridine ring opening reaction with aromatic amines. In this case, we found that the ring

opening proceeded smoothly under solvent free conditions even in the absence of $Cu(OTf)_2$. A variety of non-activated aziridines were opened with different aromatic amines. Aliphatic amines failed to open aziridines under these conditions.



Chapter 2 deals with epoxidation of α,β-enones under triphase catalysed conditions. We have prepared two polymer anchored quaternary ammonium salts **16** and **17** by heating Merrifield resin with DABCO and TMEDA respectively. Catalyst **16** was found to be more efficient than the catalyst **17** in the epoxidation of chalcone.



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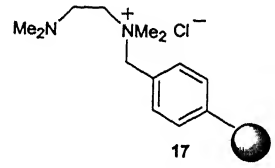

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A variety of α,β-enones were transformed to the corresponding epoxides with 10 mol% of catalyst **16** using 30% aq H_2O_2 and LiOH. We have also attempted the asymmetric version of this epoxidation reaction by using polymer anchored cinchona alkaloid based phase transfer catalysts.

Table of Contents

List of Abbreviations Used

Anal. Calcd.	Analytically calculated
BOP	Bis(2-oxo-3-oxazolidinyl) phosphonic
Bn	Benzyl
CAN	Ceric ammonium nitrate
Cat.	Catalytic
CDI	Carbonyl diimidazole
m-CPBA	*m*-Chloroperbenzoic acid
Cbz	Carbobenzyloxy
CM	Cross metathesis
DABCO	1,4-Diazabicyclo[2.2.2]octane
DCC	*N,N*-Dicyclohexylcarbodiimide
DHP	Dihydropyran
DEAD	Diethyl azadicarboxylate
DIAD	Diisopropyl azadicarboxylate
DIC	*N,N*-Diisopropylcarbodiimide
DMAP	(4-Dimethylamino) pyridine
DMF	*N,N*-Dimethyl formamide
DNP	2,4-dinitrophenylhydrazine
ee	enantiomeric excess
EI	Electron Impact
EtOAc	Ethyl acetate
FAB	Fast Atom Bombardment

FT	Fourier transform
HMPA	Hexamethylphosphoramide
IR	Infrared spectroscopy
LDA	Lithium diisopropylamide
mp	Melting point
NaHMDS	Sodium hexamethyl disilazide
NMR	Nuclear magnetic resonance
NBS	*N*-Bromosuccinimide
MEM	Methoxy ethoxymethyl
PMB	*p*- Methoxy benzyl
ppm	Parts per million
Py	Pyridine
rb	Round bottom
RCM	Ring closing metathesis
ROMP	Ring opening metathesis polymerization
rt	Room temperature
TBAF	Tetrabutyl ammonium fluoride
TBDMS	*tert*-Butyldimethylsilyl
Tf	Trifluoromethanesulfony
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TMS	Tetramethylsilane
TLC	Thin layer chromatography
p-TSA	*p*-Toluene sulfonicacid
vacuo	Vacuum

This thesis is divided into two parts; **Part A** and **Part B**.

Part A deals with "an approach towards synthesis of naturally occurring lactones *via* ring closing metathesis". Part A is sub-divided into three chapters.

Chapter 1: General introduction on ring closing metathesis (RCM).

Chapter 2: An approach towards synthesis of (-)-acaterin and (S)-fugomycin using RCM.

Chapter 3: A RCM based approach towards synthesis of (+)-diplodialide A and antimycin A_3.

Part B deals with "development of methodologies under solvent free and triphasic conditions. Part B is sub-divided into two chapters.

Chapter 1: Thioacetalization of carbonyl compounds and aziridine ring opening with aromatic amines under solvent free conditions.

Chapter 2: Triphase catalysis in epoxidation of α,β-enones using polymer anchored quaternary ammonium salts.

Part A

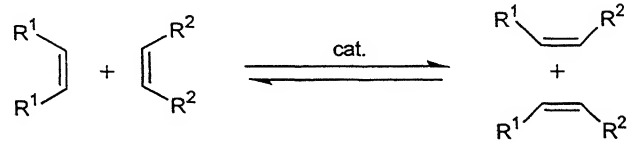
An approach towards synthesis of naturally occurring lactones *via* ring closing metathesis

Chapter 1

General introduction on Ring Closing Metathesis

1.1. Introduction:

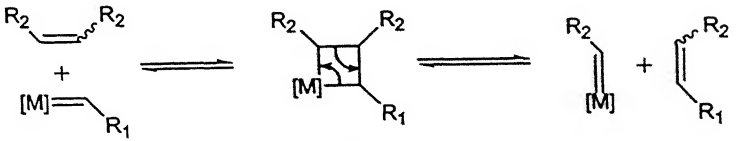
Olefin metathesis[1] is one of the most fascinating reactions in which two olefins undergo bond reorganization leading to the redistribution of alkylidine moieties (Scheme 1.1). In other words, the metathesis constitutes a catalytic method for both cleaving and forming C-C double bonds.



Scheme 1.1

Fundamental studies towards the understanding of this reaction were performed by Calderon and coworkers. They coined the term "olefin metathesis" in 1967, after they recognized that both ring-opening polymerization and the disproportionation of acyclic olefins were the same.[2] By investigating the conversion of labeled olefins, it was demonstrated that an exchange of alkylidine groups occurs during metathesis. At first it was assumed that the alkylidine rearrangement proceeds through a bis(alkylidine)metal intermediate in which both olefin ligands are coordinated to the metal atom.[3] Later Chauvin *et al.* recognized that the reaction proceeds *via* a metallo-cyclobutane intermediate (Scheme 1.2).[4] According to these ideas, olefin metathesis proceeds by a [2+2] cycloaddition between a C-C double bond and a

metal carbene complex followed by cycloreversion. In this process the fundamental steps are frequently reversible and the reaction is under thermodynamic control. The double bond formation generally does not proceed under stereocontrol and *E/Z* mixture of olefins results as metathesis products.



Scheme 1.2

The number of applications of this reaction has dramatically increased in the past few years. Of particular significance, metathesis utilizes no additional reagents beyond a catalytic amount of metal carbene and the only other product from the reaction is, in most cases, a volatile olefin such as ethylene. A number of reviews have been published in this area, all of which focus on the ever-increasing uses of olefin metathesis in organic synthesis and polymer chemistry.[5]

Olefin metathesis can be utilized in three closely related types of reactions namely,

a) Ring Opening Metathesis Polymerization (ROMP),

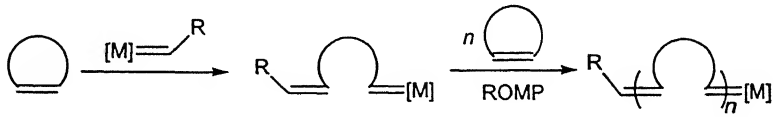
b) Ring Closing Metathesis (RCM) and

c) Cross Metathesis (CM).

1.1.1 Ring Opening Metathesis Polymerization (ROMP):

Until recently, olefin metathesis was applied almost exclusively

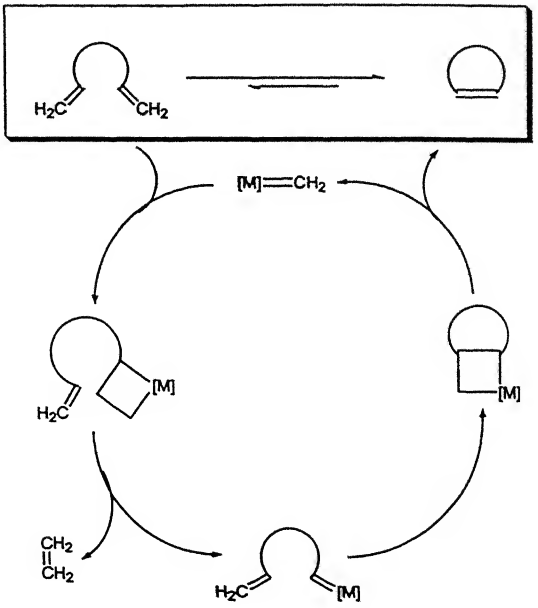
in ring opening metathesis polymerization reactions (ROMP).[6] A schematical representation of ROMP is given in Scheme 1.3. The metathetic opening of strained cyclic olefins to give open chain metal carbene complexes provides the basis of ROMP. The polymerization is induced by the conversion of an intermediate metal-carbene species with another molecule of the cycloolefin.



Scheme 1.3

1.1.2 Ring Closing Metathesis (RCM):

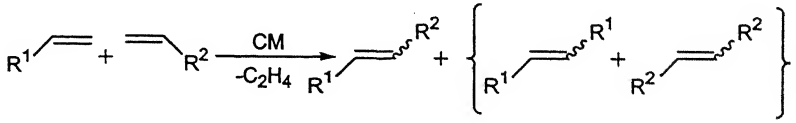
Since olefin metathesis is a reversible reaction, it is necessary to shift this equilibrium in one direction in order to make metathesis productive in preparative terms. One of the major ways to do this is Ring Closing Metathesis (RCM), which involves cyclization of α,ω-diolefins to cyclic olefins in the presence of metal carbenes (Scheme 1.4). In this particular case, the forward process is entropically driven because RCM cuts one substrate molecule into two products. If one of them is volatile (ethylene, propene etc.) the desired cycloalkene will accumulate in the reaction mixture. Although the first example was reported in 1980 by Tsuji,[7] catalytic ring closing metathesis (RCM)[8] has only recently emerged as an effective strategy in organic synthesis.



Scheme 1.4

1.1.3 Cross Metathesis (CM):

Cross metathesis[8f,i] between two acyclic olefins offer interesting possibilities for synthesizing higher-substituted alkenes. The use of highly substituted asymmetric olefins is not practical because of the expected complex spectrum of products. Use of terminal olefins results in the formation of volatile ethylene as a by-product, which provides the driving force for the reaction. This reaction (CM) is generally not stereoselective (Scheme 1.5).



Scheme 1.5

1.2 Catalysts:

1.2.1 Background:

From the mid-1950s to the early 1980s, all olefin metathesis was accomplished with poorly defined, multicomponent homogeneous and heterogeneous catalyst systems. These systems consisted of transition metal salts combined with main group alkylating agents or deposited on solid supports. Some of the classic combinations include WCl_6/Bu_4Sn, $WOCl_4/EtAlCl_2$, MoO_3/SiO_2 and Re_2O_7/Al_2O_3, among many others.[9] The utility of these catalysts, however, was limited by the harsh conditions and strong Lewis acids that they required and that made them incompatible with most functional groups. After Chauvin proposed that the metathesis proceeds *via* metallo-carbene and metallo-cyclobutane complexes, subsequent efforts have been made in the development of new catalysts during the late 1970s and early 1980s. These new catalysts included $(CO)_5W{=}CPh_2$,[10] bis(cyclopentadienyl) titanocyclobutanes,[6d] tris(aryloxide)tantalacyclobutanes,[11] and various dihaloalkoxide-alkylidine complexes of tungsten.[12]

The molybdenum and tungsten alkylidenes of the genaral formula $(NAr)(OR')_2M{=}CHR$ (Figure 1.1) were the first of these catalysts to become widely used, particularly the molybdenum complex **1a**.[13]

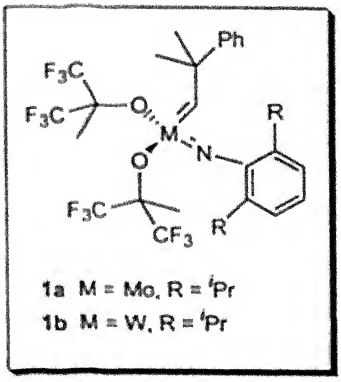
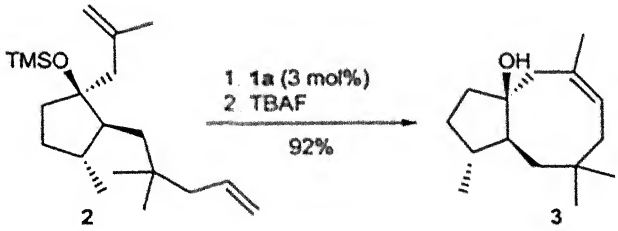


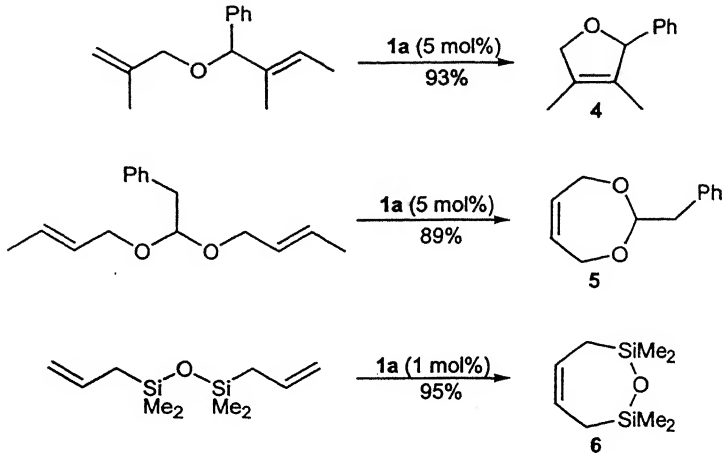
Figure 1.1

The most impressive feature of **1a** is its high activity, which allows it to react with both terminal and internal olefins and to polymerize low-strain monomers, as well as to ring-close sterically demanding and electron poor substrates.[14] For example, complex **1a** was used in the synthesis of dactylol **3**, a terpene natural product.[15] The diene **2** on exposure to **1a** provided the target natural product **3** in 92% yield, after desilylation of the crude product (Scheme 1.6).



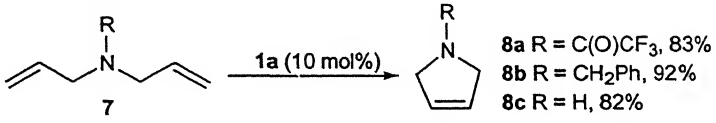
Scheme 1.6

The most comprehensive studies on oxacycle formation using catalyst **1a** were done by Grubbs,[16a] whose group has made 5-, 6- and 7 membered rings in good to excellent yields (*e.g.*, **4-6**, Scheme 1.7).



Scheme 1.7

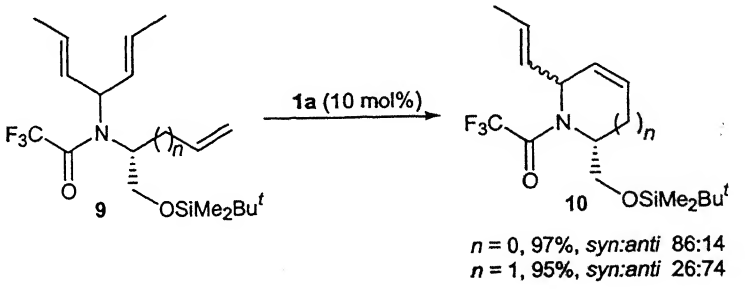
The formation of nitrogen containing rings by RCM has attracted considerable attention, not least because of their prevalence in naturally occurring systems. The initial work was carried out by Grubbs group[16b] with over 30 different azacycles reported to have been made using molybdenum catalyst **1a**. The original study demonstrated the tolerance of the catalyst for tertiary amides **8a**,[16b] tertiary amines **8b** and secondary amines **8c** (Scheme 1.8).[17]



Scheme 1.8

In an interesting development, Blechert has shown how steric effects can be harnessed to make the catalyst diastereoselective, albeit in a rather specialized systems.[18] He used the substitution pattern of the substrate to ensure that the catalyst first reacts with a terminal alkene,

and then selects, in a diastereoselective fashion, between two disubstituted alkenes to close the ring in amide **10** (Scheme 1.9).



Scheme 1.9

However, the catalyst **1a** and others based on early transition metals are limited by the high oxophilicity of the metal centres, which renders them extremely sensitive to oxygen and moisture. As an example, the synthesis and handling of **1a** requires an inert atmosphere and rigorously purified, dried and degassed solvents and reagents.[16] It is noteworthy that the corresponding tungsten catalyst **1b**, although active and widely used for polymerization, has only rarely reported to carry out ring closure.[16a,19]

1.2.2 Functional Group Tolerance: Why Ruthenium?

The disclosure of Grubbs that ruthenium carbene complexes of general type **11** (Figure 1.2) are highly active catalysts for all types of alkene metathesis reactions denoted a real breakthrough and has triggered an avalanche of interest in this transformation.[20] Although their activity is usually lower than that of Schrock's catalyst **1a**, the spectacular tolerance of these late transition metal complexes towards an array of functional groups and the ease of handling caused by a

reasonable stability against oxygen, water and minor impurities in the solvents render them exceedingly practical tools and explain their unrivaled popularity in the organic and polymer chemist communities.[8]

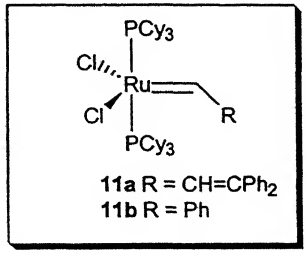
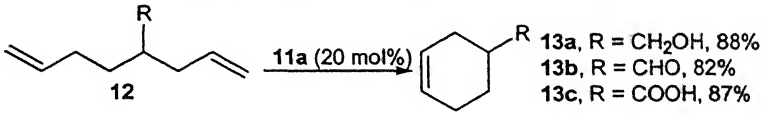


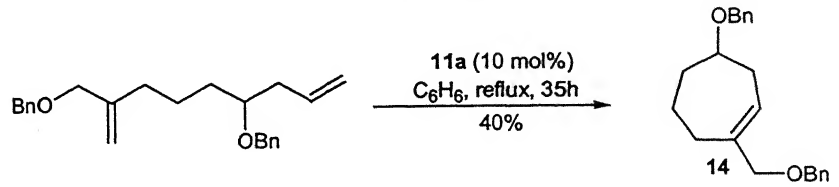
Figure 1.2

The ruthenium carbene **11a** is significantly easier to make and handle than complex **1a**. This robust catalyst is air-stable as a solid and retains its activity even when exposed to water, alcohols or acids. Grubbs reported the synthesis of a few 5- and 6-membered carbocycles having not only pendant silyl ether, but also alcohol (**13a**), aldehyde (**13b**) and carboxylic acid (**13c**) functional groups which are totally incompatible with the molybdenum catalyst **1a** (Scheme 1.10).[20c]



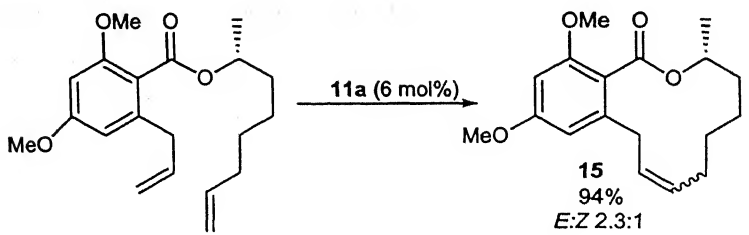
Scheme 1.10

Maier *et al.* showed that ruthenium catalyst **11a** was superior to the molybdenum catalyst **1a** for making cycloheptane **14** having a trisubstituted double bond, although the yield of the product **14** was not good (Scheme 1.11).[21]



Scheme 1.11

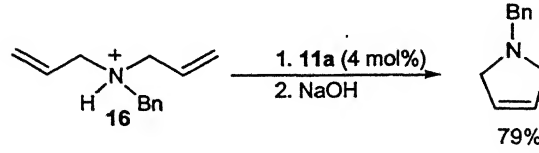
Several larger rings have been synthesized, using catalyst **11a**, as part of bi- and polycyclic systems. Fürstner *et al.*, during their synthesis of lasiodiplodin, used RCM to construct 12-membered lactone **15** in excellent yield (Scheme 1.12).[22] The *E/Z* selectivity was poor, but this was unimportant since the double bond was subsequently removed by catalytic hydrogenation.



Scheme 1.12

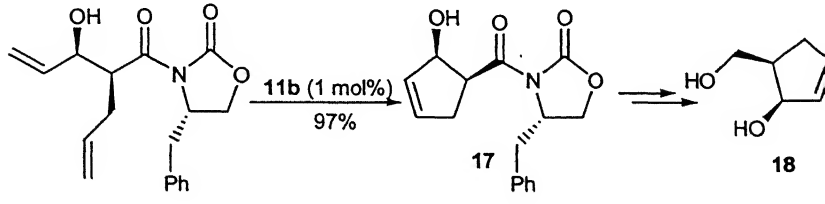
The main drawback of the ruthenium catalyst **11a** is that enol ethers are not cyclized by this catalyst, but undergo slow dimerization instead.[23] Also catalyst **11a** is incompatible with free amines[17] and sulfides[24] present in the substrate. This may be due to coordination of the substrate onto the ruthenium center. In case of amines, this problem can be solved by protecting the amine as a carbamate, or more simply

by protonating the amine: for example, ammonium salts such as **16** are suitable substrates for catalyst **11a** (Scheme 1.13).[20c]



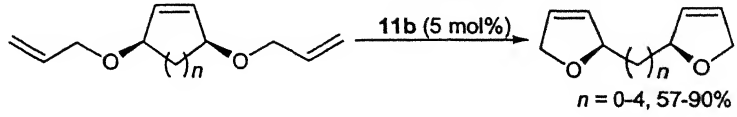
Scheme 1.13

Since, the organic precursor for catalyst **11a** is diphenyl cyclopropane, which is very difficult to synthesize, the application of this catalyst is limited. The ruthenium carbene **11b** is the modification of **11a** and has been prepared in a straight forward fashion from readily available phenyl diazo methane.[25] Also, **11b** was proved to be more active catalyst than **11a**.[25a] Like **11a**, the catalyst **11b** is air-stable and retains its activity even when exposed to water, alcohols or acids. These characteristics make catalyst **11b** ideal for a wide range of synthetic organic applications. For example, the successful and high yielding synthesis of cyclopentenol **18** *via* the intermediate **17** demonstrates the compatibility of the catalyst **11b** with free alcohols as well as with carbonyl groups in the substrate, and also the suitability of this catalyst for making optically active compounds (Scheme 1.14).[26]



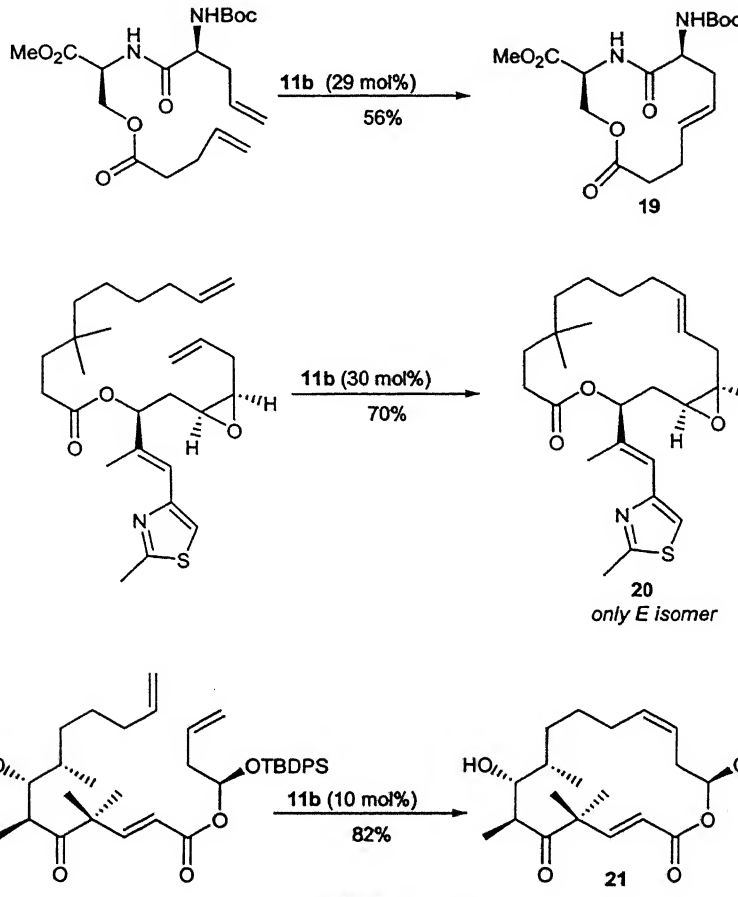
Scheme 1.14

Grubbs and co-workers have demonstrated the potential of benzylidine complex **11b** for the sequential opening of one unsaturated ring and closure of two more within the same molecule. This *tandem ring opening-ring closing process* was expected to be assisted by starting from a small, strained cycloalkene, but in fact the original ring may be any size from four- to eight-membered (Scheme 1.15).[27]



Scheme 1.15

The catalyst **11b** was applied to the synthesis of many medium and large ring compounds. Twelve-membered (*e.g.*, **19**, Scheme 1.16)[28] and sixteen-membered rings have been successfully synthesized by using **11b**. The groups of Danishefsky[29] and Nicolaou[30] utilized the ruthenium carbene **11b**, in their approaches to the synthesis of epothilone group of natural products (Scheme 1.16). The successful formation of these lactones demonstrates the compatibility of ruthenium benzylidine **11b** with epoxides (*e.g.*, **20**) and free alcohols (*e.g.*, **21**) as well as with various silyl ethers in the substrate. It was also demonstrated that the metal carbene **11b** will metathesise terminal alkenes while leaving intact internal di- or tri- substituted alkenes (*e.g.*, **20**, **21**) elsewhere in the molecule.

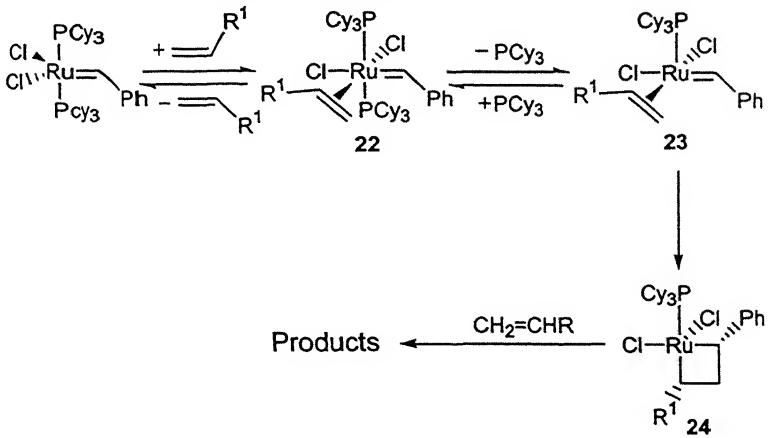


Scheme 1.16

1.2.3 Mechanistic Studies:

Grubbs and co-workers have proposed a mechanism of ruthenium carbene catalyzed RCM, based on extensive kinetic studies.[31] As illustrated in Scheme 1.17 the first step involves olefin coordination to the metal center, presumably *cis* to the alkylidine. The phosphine dissociation and the alkylidine rotation occur in order to generate the 16-electron intermediate **23**, in which the olefin remains

cis to the alkylidine. This intermediate then undergoes metallo-cyclobutane **24** formation *cis* to the bound phosphine, followed by cleavage to release the metathesis products.



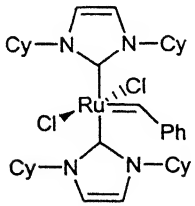
Scheme 1.17

The catalytic activity of metathesis reaction increases with larger and more electron-donating phosphines and decreases with larger and more electron donating halides. The main contribution of phosphine ligands is σ- donation to the metal center, which promotes formation of mono-(phosphine) olefin complex by facilitating phosphine dissociation and stabilizing the vacant trans site in **23**.[32] Perhaps even more importantly, helps stabilize the 14-electron metallo-cyclobutane intermediate **24**.

1.2.4 Recent Developments in Catalyst Design:

As we discussed earlier, $(PCy_3)_2Cl_2Ru$=CHPh (**11b**) forms a highly active mono(phosphine) intermediate during the catalytic cycle. As a design motif, this intermediate became a starting point for the

development of improved catalysts. The two important factors involved in the catalytic activity of ruthenium carbene are as follows. First, for olefin metathesis to begin, at least one of the ancillary ligands must be labile enough for catalyst activation. Second, because decomposition of **11b** is known to be second order and inversely proportional to phosphine concentration, it is generally important to maintain a low concentration of mono (phosphine) species. Herrmann and co-workers have found that *N*-heterocyclic ruthenium carbene **25** (Figure 1.3) showed little improvement in activity compared to **11b**.[33] But it is well known that, compared to phosphines, *N*-heterocyclic carbene ligands are stronger σ- donors and much less labile.[34] As a result, the *N*-heterocyclic carbenes in **25** are not able to readily dissociate. So a mixed ligand complex could overcome this problem in two ways. Initially, the more strongly electron-donating carbene ligand might enhance the dissociation of the more labile trans phosphine from the metal center. Then, by virtue of its steric bulk and the electron donating properties, the same ligand should more effectively stabilize the electron-deficient intermediates and promote olefin metathesis.



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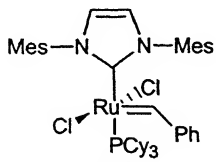

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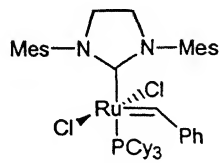
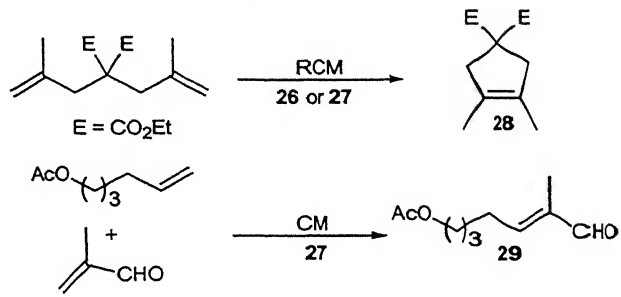


27

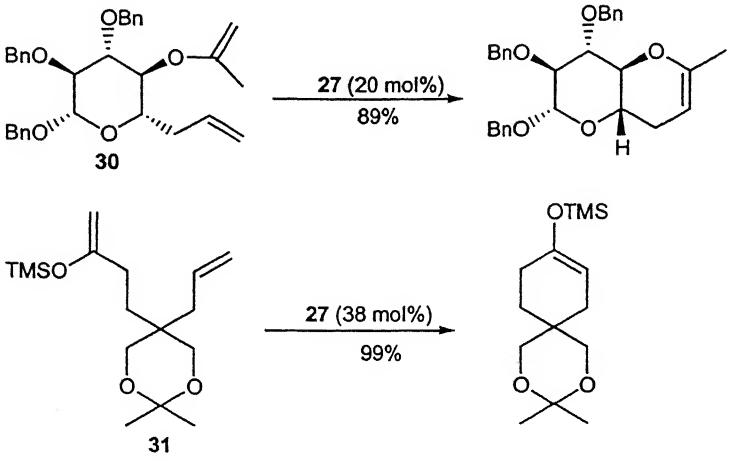
Figure 1.3

After exploring a variety of ligand derivatives, Grubbs and co-workers found that a mesityl-substituted *N*-heterocyclic carbene worked well. They showed that **26**[35] and **27**[36] showed better activity than **25**. Both **26** and **27** are able to perform RCM of sterically demanding dienes to form tri- and tetra-substituted olefins (*e.g.*, **28**, Scheme 1.18).[35] In addition, catalyst **27** produced the first example of CM to yield a trisubstituted olefin (e.g., **29**, Scheme 1.18).[37]



Scheme 1.18

Moreover, the catalyst **27** is highly efficient for the ring closure of enol ethers[42] (*e.g.*, **30**, Scheme 1.19) and silyl enol ethers[43] (*e.g.*, **31**, Scheme 1.19), which are generally problematic substrates for the catalysts **11a** and **11b**. Until now, it had seemed that functional group tolerance was gained at the expense of activity. The "*next generation*" catalysts **26** and **27**, however, rival the activity of early metal catalysts such as **1** and retain the functional group tolerance of **11b**. Other ruthenium-based catalysts (**32-35**) that are used for olefin metathesis are listed in Figure 1.4.



Scheme 1.19

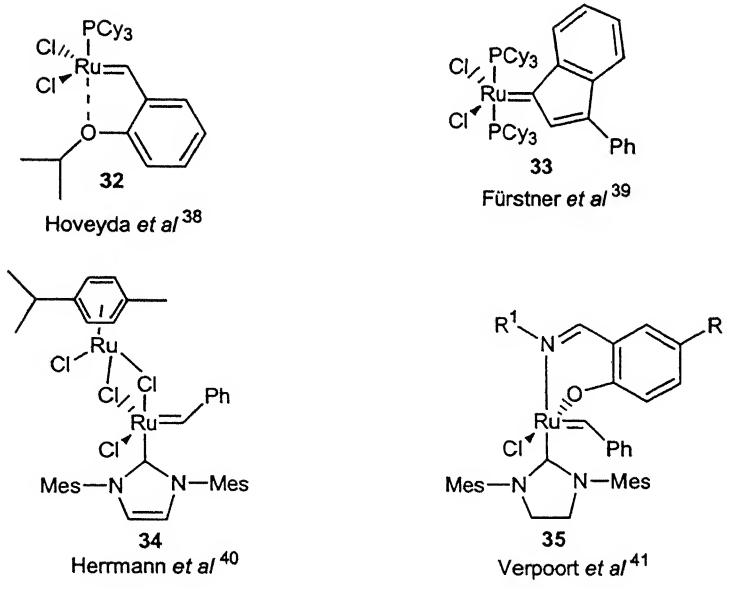


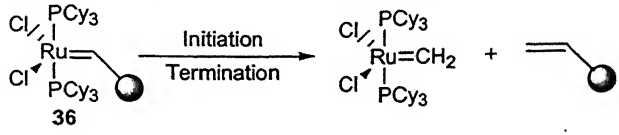
Figure 1.4

1.2.5 Solvents and reaction conditions:

The common solvents that used for RCM include CH_2Cl_2, benzene and toluene. Generally RCM reaction can be performed either at room temperature or at reflux temperature depending upon nature of the substrate. Since intermolecular dimer formation always competes with the intramolecular RCM, it is better to perform the RCM reaction under high dilution conditions.

1.2.6 Purification of the reaction mixtures:

The products result from RCM may, however, still contain traces of metal salts derived from the catalyst. Grubbs has recently developed an improved work-up procedure which involves the addition of excess tris(hydroxy methyl)phosphine to the crude mixture.[44] This ligand forms a water soluble complex and subsequently removed by simple aqueous work up. Other methods for the removal of ruthenium impurity include the treatment of crude product with $Pb(OAc)_4$,[45] Ph_3PO or DMSO.[46] Another innovative possibility of removing the ruthenium impurity was explored by Barrett and co-workers who anchored the ruthenium catalyst on to a insoluble polymer support (Scheme 1.20).[47] The carbene substituent of the immobilized precatalyst **36** is cleaved off during the first turn of the catalytic cycle and the ruthenium template is, thereby, released from the polymer and acts as a homogeneous catalyst; it is, however recaptured by the resin once the substrate in the solution has been consumed. The authors have coined the expression "*boomerang catalyst*" which nicely describes the overall behavior.



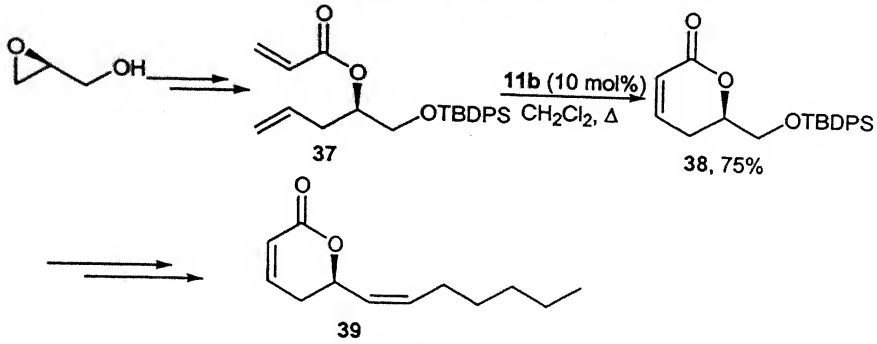
Scheme 1.20

1.3 Selected Application to Natural Product Synthesis:

As a result of the pronounced tolerance to many different functional groups, metal carbene catalyzed RCM has increasingly been used in the area of natural product synthesis. Since the applications of RCM in natural product synthesis have been reviewed in many review articles[8] until the year 2001, we wish to discuss here the very recent literature of RCM to the synthesis of natural products.

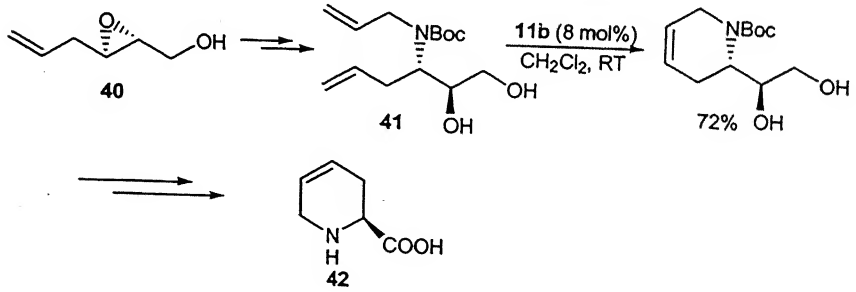
1.3.1 Small and medium rings formation:

Many biologically important natural products, consisting of small and medium rings, have been synthesized by utilizing RCM as the key step. Very recently, Hansen reported a facile synthesis of (-)-argentilactone **39**, an antileishmanial agent, starting from the commercially available (*S*)-glycidol, that utilizes a RCM reaction as the key step (Scheme 1.21).[48] The diene ester **37** derived from (*S*)-glycidol on cyclization with catalyst **11b** provided the unsaturated δ-lactone **38** in 75% yield, which could be transformed to (-)-argentilactone **39** in just 2 steps.



Scheme 1.21

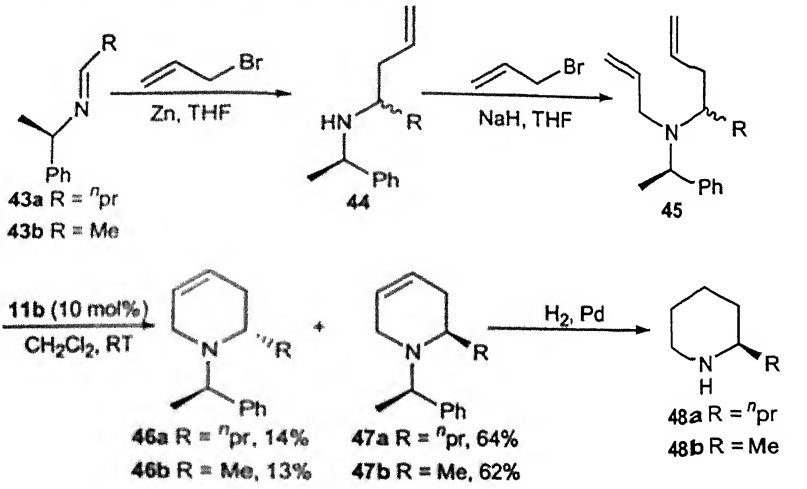
Pericàs *et al*, have reported a RCM based approach to the enantioselective synthesis of baikiain **42** using readily available enantiopure 2,3-epoxy-5-hexen-1-ol **40** as the starting material.[49] The regio- and stereoselective ring opening of the epoxide ring by allyl amine followed by *N*-protection with Boc_2O afforded the diene intermediate **41** which was subjected to RCM. The product, thus, obtained as a result of RCM was converted in to baikiain **42** by known simple steps (Scheme 1.22).



Scheme 1.22

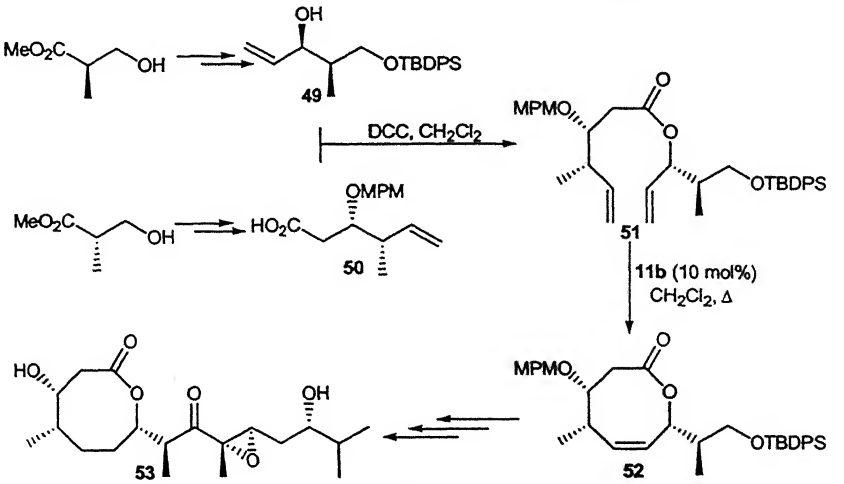
Recently, a concise synthesis of (-)-coniine **48a** and (-)-pipecoline **48b** using a RCM strategy has been reported.[50] The

synthesis of **48a** and **48b** has been achieved starting from imines **43a** and **43b** which were, in turn, derived from butanal and acetaldehyde respectively using (*R*)-α-methyl benzylamine as a chiral auxillary (Scheme 1.23). The diene **45** was obtained from **43** by *C*-allylation followed by *N*-allylation. The ring closure of **45** using **11b** gave the carbocycles in which the desired isomers **47a** and **47b** were obtained as major products. The carbocycles **47a** and **47b**, on reduction with H_2/Pd gave the alkaloids (-)-coniine **48a** and (-)-pipecoline **48b** respectively. This synthesis clearly shows that the catalyst **11b** is highly efficient for RCM even in the presence of free amines.



Scheme 1.23

RCM has been successfully applied to the synthesis of many medium size natural products. For example, octalactin A **53**, an eight membered naturally occurring anticancer agent, has been synthesized from a readily available (*R*)- and (*S*)- 3-hydroxy-2-methyl propionates.



Scheme 1.24

The alcohol **49** and the acid **50** were derived from (*R*)- and (*S*)-3-hydroxy-2-methyl propionates respectively. The condensation reaction between **49** and **50** in the presence of DCC provided the diene ester **51**, which was subsequently cyclized in the presence of ruthenium carbene **11b** to give the unsaturated lactone **52** (Scheme 1.24). The lactone **52** was converted in to octalactin A in a series of steps.

Figure 1.5 shows a list of some of the natural products that have been synthesized by using RCM as the main step. In all these structures in Figure 1.5, the bond formed as a result of RCM is represented in dark lines.

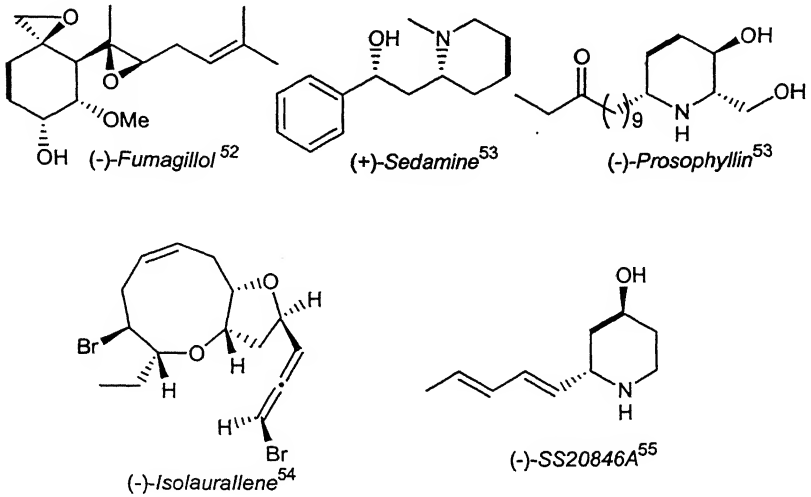
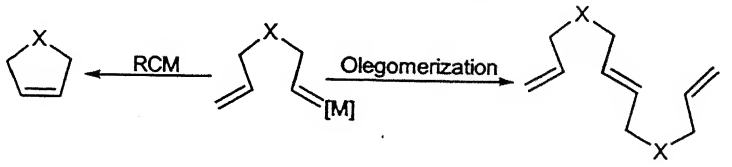


Figure 1.5

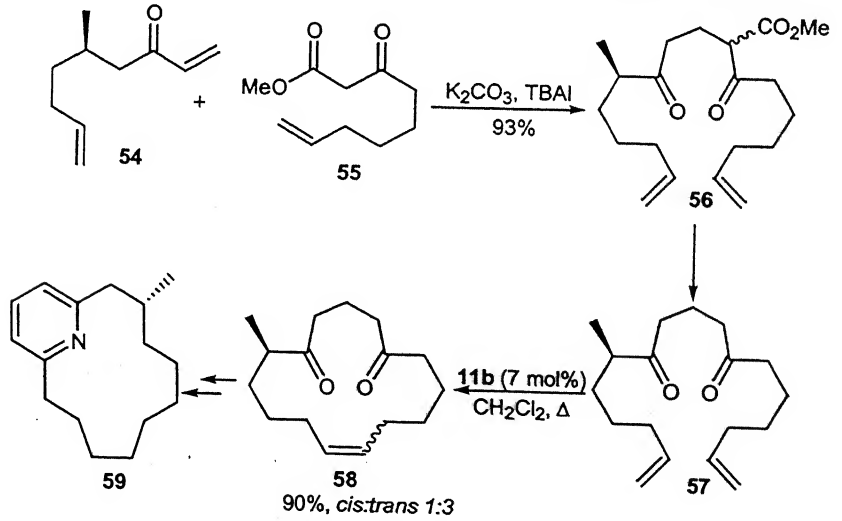
1.3.2 *Macrocycles formation*:

One of the major considerations for RCM in the synthesis of large ring systems is the conformational predisposition of starting material for favorable intramolecular cyclization. The rate of ring closure decreases due to ring size and conformational effects, and the competing reactions, like olegomerization etc., interfere the desired reaction (Scheme 1.25). The rate of olegomerization can be decreased by lowering the concentration of the diene or using slow addition of the substrate. Higher temperatures also favor ring closure. However, both of these factors, low concentration and high temperature, which favor closure, also allow the catalyst to decompose. As a result, closure of larger rings usually requires higher catalyst loading.



Scheme 1.25

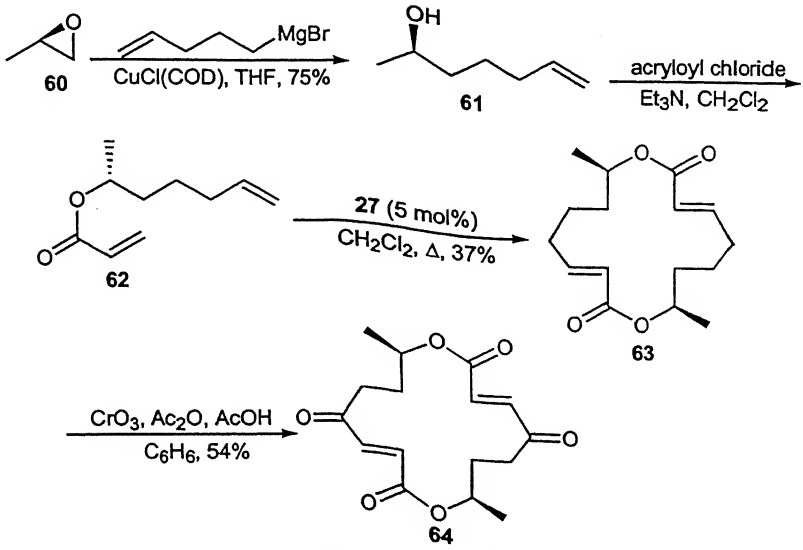
Recently, Hagiwara reported the first synthesis of (*R*)-(+)-muscopyridine **58**, a 13-membered natural perfumery agent, using RCM as a key step (Scheme 1.26).[56] The keto-alkene **54** was readily prepared from (*R*)-(+)-citronellal. Michael addition of the β-keto ester **55** to the vinyl ketone **54** under PTC conditions afforded the β-keto ester **56**, which was subsequently subjected to decarboxylation to give 1,5-dicarbonyl product **57**. Cyclization of **57** was achieved by using



Scheme 1.26

Grubbs carbene **11b** under reflux conditions in CH_2Cl_2 to provide the desired 15-membered diketone **58** as a 3:1 mixture of isomers in 90%

yield. The major isomer was identified as *E* from ^{1}H NMR signals. The diketone **58** was then transformed to (*R*)- muscopyridine **59** through a series of steps.



Scheme 1.27

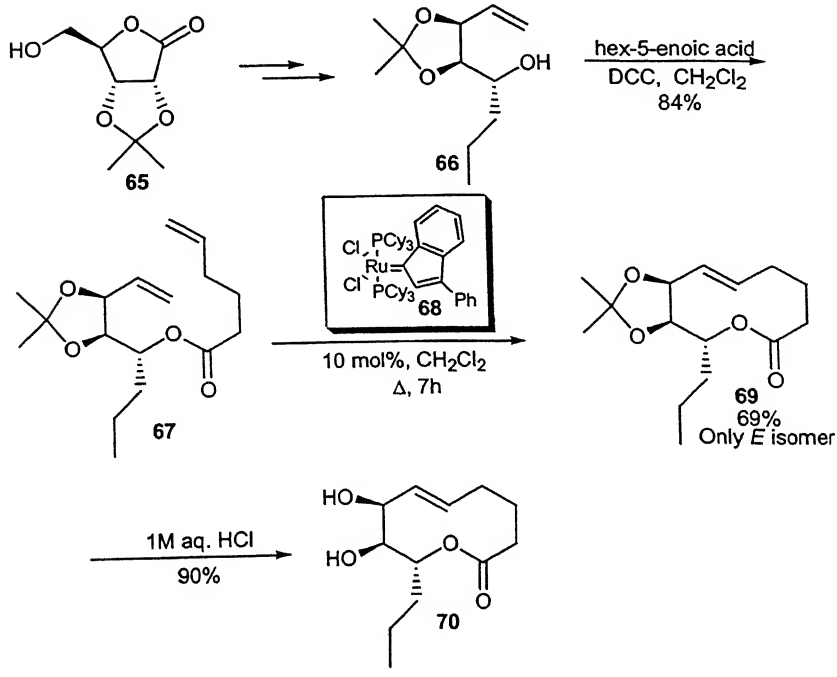
Fürstner and co-workers reported a shortest route to the synthesis of (-)-pyrenophorin **64**, a 16-membered antifungal agent, by RCM using "second generation" ruthenium catalyst (Scheme 1.27).[57] They used enantiomerically pure (*R*)-propenodide **60** as a starting material. Reaction of **60** with but-3-enylmagnesium bromide in the presence of a catalytic amount of CuCl(COD) delivered an alcohol **61** in good yield which was esterified with acryloyl chloride under standard conditions to give ester **62**. Surprisingly, however, the diene **62** on treatment with Ru complex **27** underwent smooth cycloolegomerization to yield the cyclic product **63** in 37% yield which

on oxidation with CrO_3 gave the natural product (-)-pyrenophorin **64** in 54% yield. Although the yield of the macrocyclization step was low, the overall yield obtained over the entire sequence (12%) compares well with the previous syntheses of this particular macrolide (Scheme 1.27).

Fürstner's approach[58] to herbarumin I **70**, a potent phyto-pathogenic macrolide, involves a stereo-selective construction of a 10-membered ring using ruthenium indenylidine complex **68**[59] as a RCM catalyst (Scheme 1.28). A readily available D-ribonolactone acetonide derivative **65** was used as a starting material in their approach. Subsequent transformation of **65** into **66** was achieved in 5 steps. The compound **66** on treatment with hex-5-enoic acid gave the RCM substrate **67** in good yield. The macrocyclization step was very crucial in this particular case because, as in herbarumin I, the product obtained as a result of RCM should have *E* configuration in its macrolide skeleton.

It is known in the literature that the stereoselectivity in RCM can be influenced by the nature of the protecting group adjacent to the double bond.[60] The isopropylidine acetal of compound **67** acts as a temporary constraint for the stereoselective formation of *E* isomer. Thus, the macrocyclization of the diene **67** in the presence of 10 mol% of the catalyst **68** gave the desired *E* isomer **69** as a single product. This particular example nicely features the excellent application profile of the ruthenium complex **68**, which is equivalent or even superior to the most popular Grubbs carbene **11b**. The cyclic compound **69** on

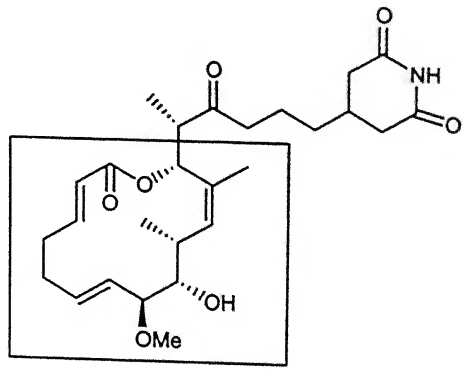
deprotection with dilute *aqueous* HCl provided herbarumin I **70** in 11% overall yield (Scheme 1.28).



Scheme 1.28

The stereoselective RCM was also observed in the synthesis of migrastatin **71** by Danishefsky and co-workers (Figure 1.6). His group used "*second generation*" Grubbs catalyst **27** for the synthesis of macrolide core **78** (highlighted in Figure 1.6) of migrastatin. Their approach to migrastatin starts from an adduct **74** derived from an aldehyde **72** and a diene **73** by a chelation controlled $TiCl_4$ catalysed hetero Diels-Alder reaction (Scheme 1.29). The adduct **74** was

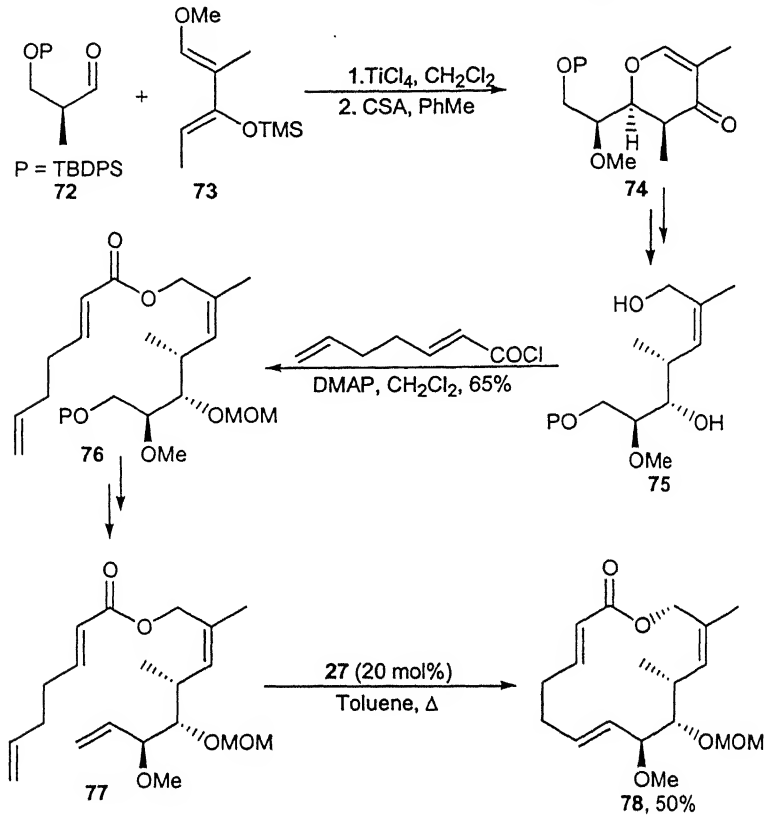
successfully transformed to the diol **75** which was selectively esterified with hept-1,6-dienoic acid in the presence of DMAP to give the ester **76** in 65% yield. A simple 3-step sequence (deprotection of silyl ether and oxidation by Dess-Martin periodane followed by olefination by Tebbe's reagent) provided to metathesis precursor **77**, which was subjected to RCM with 20 mol% of the ruthenium carbene **27** in refluxing toluene (0.5 mM) to yield the desired macrolide **78** as a single olefinic isomer (the (*E*)-congener) (Scheme 1.29).



Migrastatin
71

Figure 1.6

Noteworthy, treatment of **77** with the first generation Grubbs catalyst **11b** in refluxing CH_2Cl_2 led exclusively to the dimeric product derive from cross metathesis of the terminal double bond of the acyl moiety. The high olefinic stereoselectivity in RCM reaction, in this case, might be due to the influence of the protecting group (in this case –OMe) adjacent to the olefinic double bond.



Scheme 1.29

Figure 1.7 shows the list of naturally occurring macrolides which were prepared through RCM. In all these structures, the bond formed as a result of RCM is represented in dark lines.

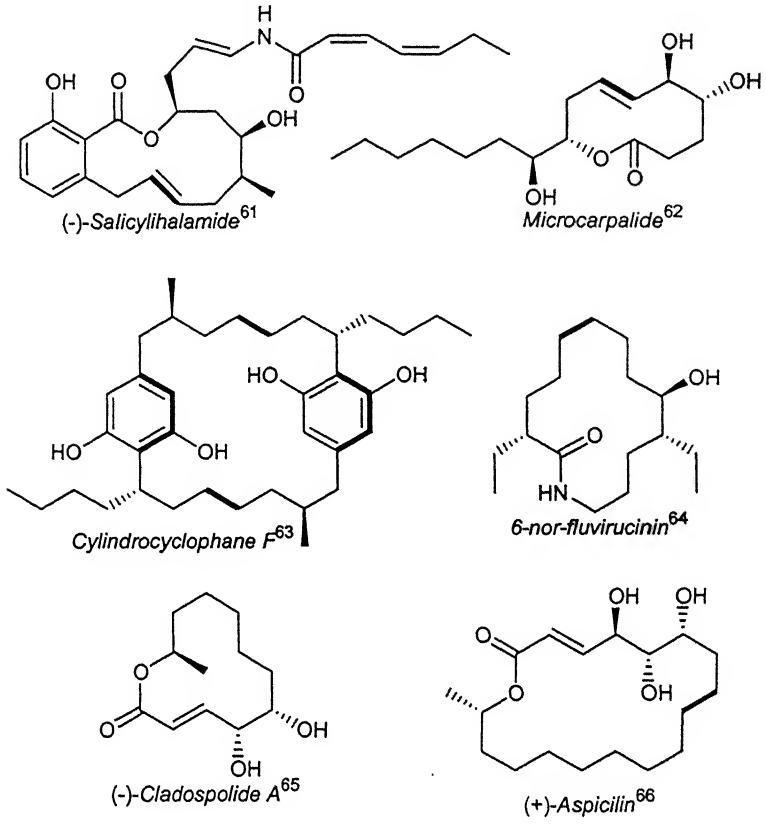
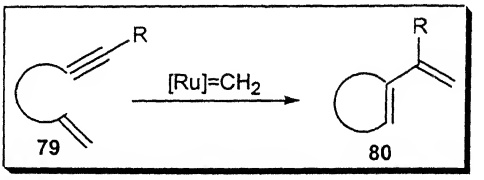


Figure 1.7

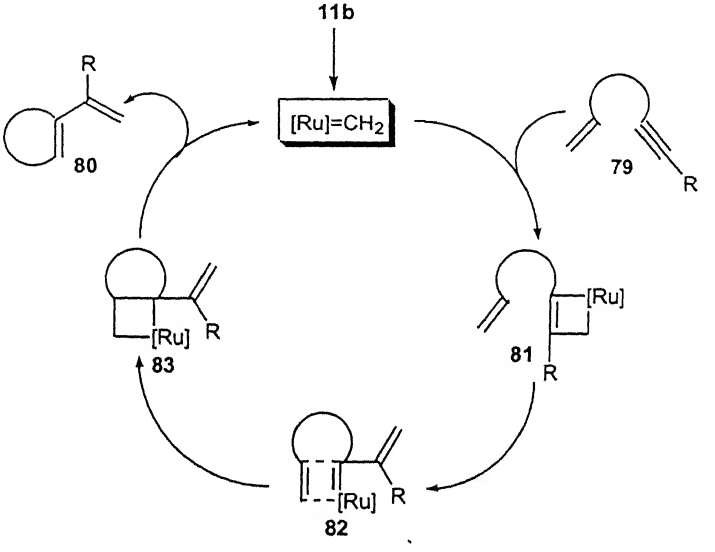
1.3.3 Ring formation by Enyne Metathesis:

Enyne metathesis is a very unique reaction, which involves a reaction between an alkyne and a olefin, leading to the formation of a butadiene moiety.[67,68] Formally, the reaction proceeds through the formation of a new C-C bond between the triple bond and the double bond to give a cyclized product **80**, and the alkylidine part of the alkene **79**, migrates onto the alkyne carbon to form a diene moiety (Scheme 1.30).



Scheme 1.30

The reaction course for intramolecular enyne metathesis is shown in Scheme 1.31.



Scheme 1.31

Methylidene ruthenium complex $Ru=CH_2$, which is produced from benzylidene ruthenium complex **11b**, reacts with alkyne part to form a cyclobutane derivative **81** *via* [2+2] cycloaddition. It is then converted into vinylidene-carbene complex **82**, which reacts with the olefin part in a tether to give another metallo-cyclobutane **83**, which subsequently releases the cyclized product **80** and the methylidene

ruthenium complex $Ru=CH_2$. Thus, the catalytic cycle is established. When $Ru=CH_2$ reacts first with the olefin moiety of enyne **79**, a similar catalytic cycle is represented.[69]

Mori and her co-workers have shown the applicability of enyne metathesis to the synthesis of small and medium sized rings.[67a-c] Natural products such as (-)-stemoamide[68a] and (-)-salicylihalamide[70] have been synthesized by using ring closing enyne metathesis as a key tool.

Chapter 2

An Approach Towards Synthesis of (-)-Acaterin and (*S*)-Fugomycin using Ring Closing Metathesis

2.1 Introduction

Enantiomerically pure γ-substituted α,β-unsaturated γ-lactones (γ-butenolides) form an important class of compounds which constitute pivotal building blocks for the synthesis of a wide range of biologically active compounds[71] and also appear as substructures in many natural products such as acetogenins,[72] muconolactones,[73] leptospharin,[74] and strigol.[75] Most of them have cytotoxic, antitumour, antimalarial, immunosuppressive and pesticide activities.[76] The biological activity of these natural products is mainly due to the presence of an unsaturated γ-lactone skeleton in their structures. As a consequence, considerable efforts have been made directed towards the synthesis of this kind of biologically active compounds.[77]

(-)-Acaterin **84** and (*S*)-fugomycin **85** are such naturally occurring biologically important molecules which contain α,β-unsaturated γ-butyrolactone moiety in their structure (Figure 2.1).

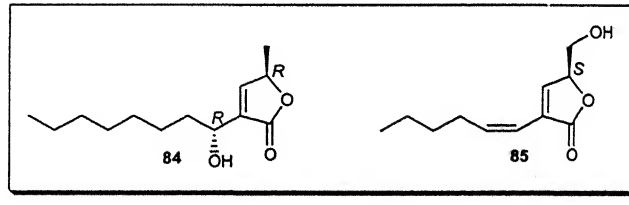


Figure 2.1

(-)-Acaterin **84**, isolated from a culture broth of *Pseudomonas* sp. A 92 by Endo and co-workers,[78] is an inhibitor of Acyl-CoA: Cholesterol Acyl Transferase (ACAT).[79] ACAT inhibitors are expected to be effective for treatment of atherosclerosis and hypercholesterolemia.[80,81] The absolute stereochemistry of natural acaterin was assigned as 4*R*, 1*R* (**84**) by Kitahara and co-workers,[82a] after synthesizing its all four possible isomers (Figure 2.2).

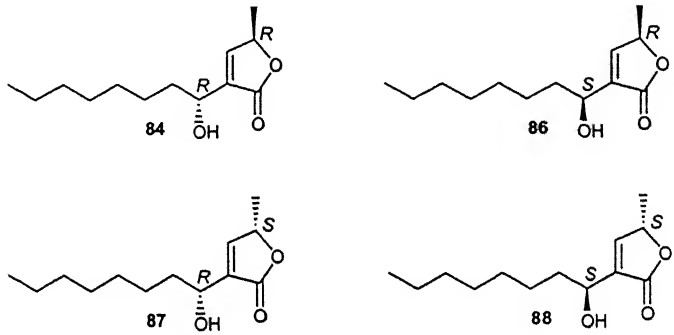
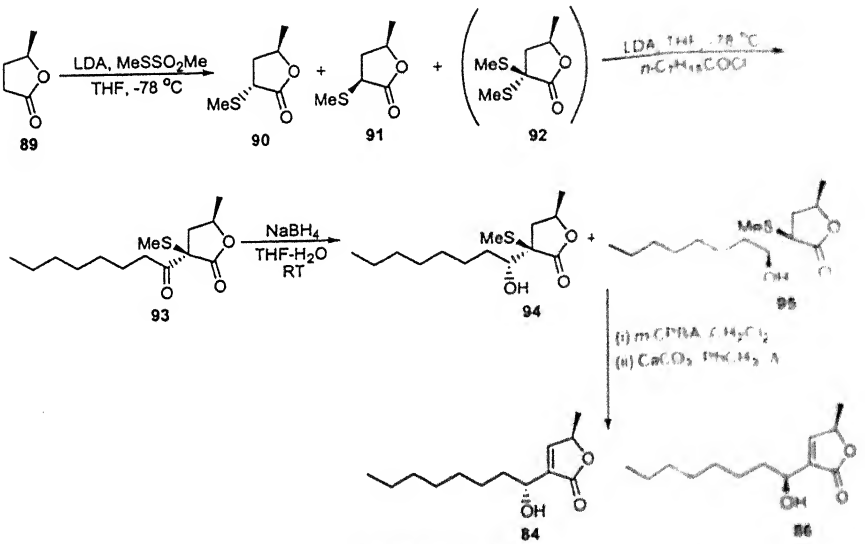


Figure 2.2

Their synthetic plan towards all isomers of acaterin is given in scheme 2.1. The starting materials used in their synthesis were (*R*)- and (*S*)-ethyl 3-hydroxybutanoate. The (4*R*, 1*R*) and (4*R*, 1*S*) isomers of acaterin were synthesized from (*R*)-ethyl 3-hydroxybutanoate. (*R*)-ethyl 3-hydroxybutanoate was readily converted into (*R*)-γ-valerolactone **89** by a known procedure.[83] Treatment of γ-valerolactone with LDA and methyl methanethiosulfonate gave a separable mixture of *trans* **90** and *cis* (**91**) sulfides along with bis-methylthio derivative **92** in 46%, 23% and 10% yields respectively. Both sulfides **90** and **91** were treated with LDA and octanoyl chloride to afford single β-keto lactone **93** in 73%

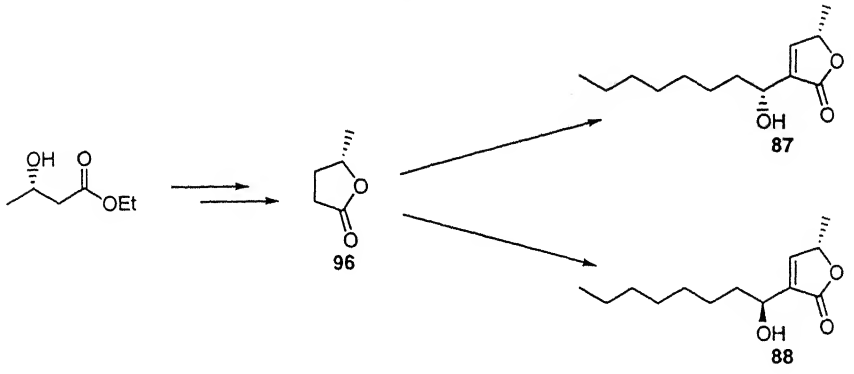
yield, which was reduced with $NaBH_4$ to give a 1:1 mixture of diastereomers **94** (42.3%) and **95** (40%). Oxidative elimination of methylthio group afforded natural acaterin **84** and (4*R*, 1*S*)-*pseudo* acaterin **86** in 64% yield.



Scheme 2.1

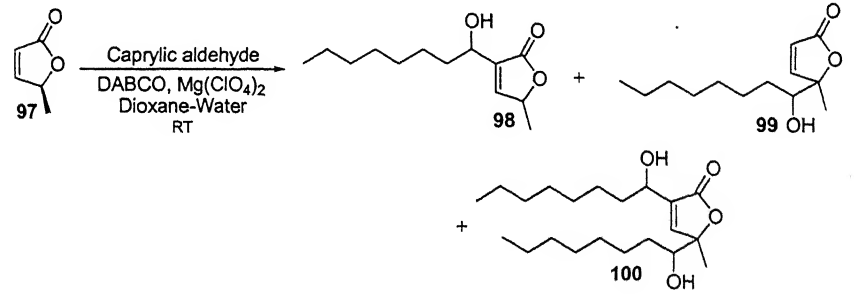
In the same manner, (*S*)-ethyl hydroxybutanoate was transformed to (*S*)-γ-valerolactone **96**, which was subsequently converted into **87** and **88** in 7.2% and 6.4% overall yields through 10 steps (Scheme 2.2).

ACAT inhibition activity of four stereoisomers of acaterin was assayed using microsomes prepared from rat liver. Interestingly, ACAT inhibitions by all the four stereoisomers were much the same.[82a]



Scheme 2.2

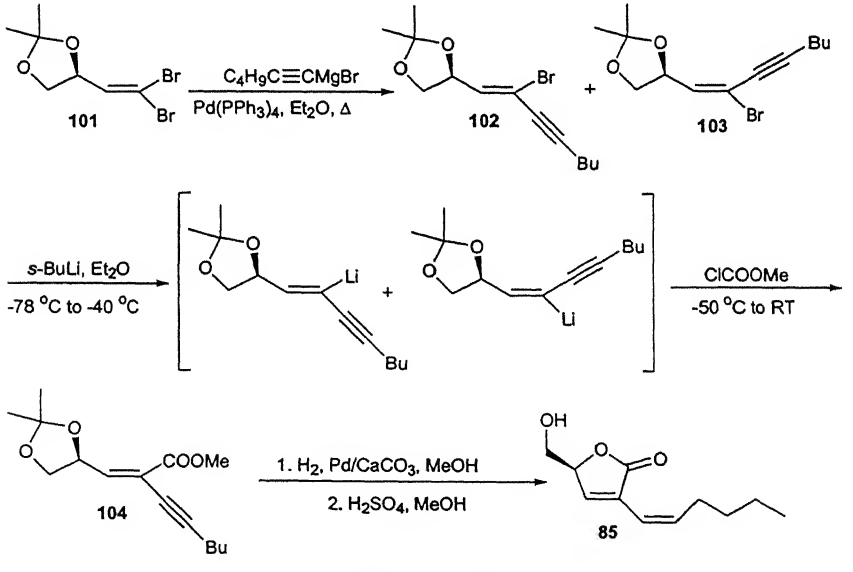
During our progress towards synthesis of acaterin, one more report has appeared in the literature, which deals with a simple one step synthesis of acaterin *via* a new application of the Baylis-Hillman reaction.[84] The starting material used was enantiomerically pure (*S*)-γ-valerolactone **97**, which was prepared by asymmetric reduction of the required α-chlorinated ketone with Baker's yeast.[85] The Baylis-Hillman reaction of (*S*)-lactone **97** with caprylic aldehyde in the presence of DABCO and $Mg(ClO_4)_2$ (additive) gave acaterin **98** in 47% yield along with by-products **99** and **100** in 11% and 10% yields respectively (Scheme 2.3).



Scheme 2.3

Although the yield of acaterin was reasonable, the ee was very poor (around 15%). It was explained that the lowering of ee is due to racemization of the (*S*)-lactone **97** in the presence of DABCO. The formation of by-products **99** and **100** also clearly shows that racemization of (*S*)-**97** was taking place under basic conditions.

Fugomycin (**85**) was isolated, very recently, from the strain 63-28 of *Pseudomonas aureofaciens* and was found to have remarkable antifungal activity.[86] The absolute configuration of fugomycin **85** was determined as "*S*" by Braun and co-workers.[87] They used readily available dibromoalkane **101** as a starting material for the synthesis of natural (*S*)-fugomycin **85** (Scheme 2.4).



Scheme 2.4

First, the dioxalane **101** was subjected to a palladium-catalyzed reaction with hexynylmagnesium bromide to give the isomeric products

102 and **103** in 4:1 ratio. These isomers **102** and **103** on bromine/lithium exchange reaction followed by treatment with methyl chloroformate delivered the carboxylic ester **104** in almost quantitative yield. Subsequently, hydrogenation in the presence of Lindlar's catalyst led to the formation of the *cis* diene which on treatment with sulfuric acid in methanol followed by lactonization provided (*S*)-fugomycin (**85**) in 11% overall yield.

2.2 Background:

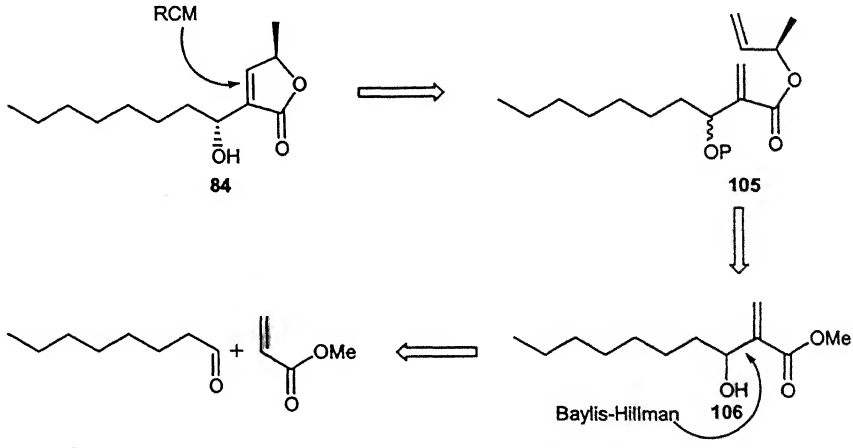
Butenolides are γ-butyrolactones with $C^{\alpha}=C^{\beta}$ bond. They abound in nature, revealing a great variety of substitution patterns. Consequently, the development of efficient routes towards enantiomerically pure butenolides has received considerable attention. One of the major ways to synthesize these compounds is through "*Chiron Approach*", starting from simple enantiomerically pure synthons such as carbohydrates and hydroxy acids. Among these two, carbohydrates have received greater attention because they are readily available and cheap.

For the past several years we have been working in the area of total synthesis of lactone natural products. We have successfully completed the syntheses of 5-hexadecanolide,[88] (+)-boronolide[89] and muricatacin[90] from readily available and inexpensive D-mannitol. This prompted us to synthesize similar kind of δ- and γ- lactone natural products. We came across many natural products having γ- or δ-lactone sub-units and chosen (-)-acaterin **84** as the target. Acaterin was isolated from *Pseudomonas* sp A92 and is having remarkable ACAT inhibition activity. It was found that the ACAT inhibition activity of all the four isomers of acaterin was the same. In this chapter we disclose a convergent synthesis of (-)-acaterin and its diastereomer **86** starting from a Baylis-Hillman adduct derived from methyl acrylate and caprylic aldehyde through ring closing metathesis (RCM). We also address our attempted efforts toward the synthesis of (*S*)-fugomycin **85**, an antifungal agent, starting from D-mannitol.

2.3. Present Work:

In recent years, RCM has become a widely applicable method for forming C-C bonds.[8] As a result of pronounced tolerance to many functional groups this method has been increasingly used in the area of natural product synthesis. Many γ-, δ- and macrocyclic lactone natural products have been synthesized using RCM as a key step. Keeping these things in mind, we started working on the total synthesis of (-)-acaterin **84** and (*S*)-fugomycin **85** by applying RCM methodology.

Our retrosynthetic strategy towards the synthesis of (-)-acaterin is presented in Scheme 2.5.

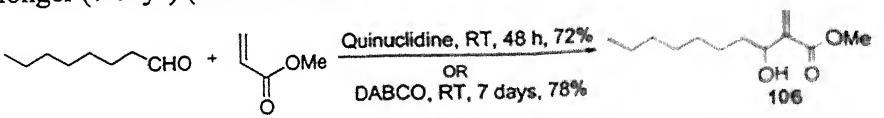


Scheme 2.5

A careful inspection of (-)-acaterin **84** reveals that the 5-membered ring of the target **84** can be constructed from an acyclic diene precursor **105** *via* RCM. The metathesis precursor **105** can be obtained from a hydroxy ester **106** through simple ester hydrolysis and

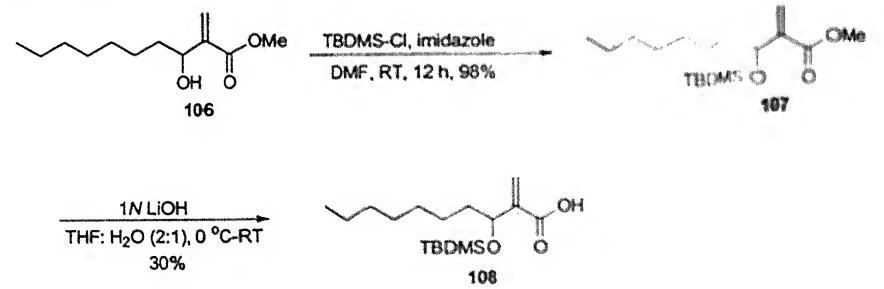
esterification steps. The hydroxy ester **106**, in turn, can be prepared by the Baylis-Hillman reaction of caprylic aldehyde with methyl acrylate.

The Baylis-Hillman reaction[91] of caprylic aldehyde with methyl acrylate in the presence of a catalytic amount of quinuclidine[92] gave an adduct **106** in 72% isolated yield. Using DABCO as a catalyst, the adduct **106** was obtained in 78% yield but the reaction time was quite longer (7 days) (Scheme 2.6).



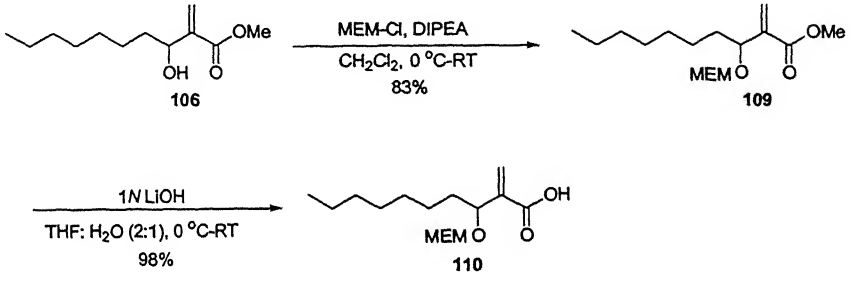
Scheme 2.6

We planned to protect the hydroxyl group of the adduct **106** and then hydrolyze the ester. We chose TBDMS ether as the protecting group. Thus, the treatment of the hydroxy ester **106** with TBDMS-Cl and imidazole in DMF gave the desired TBDMS ether protected ester **107** in 98% yield. It was observed that the hydrolysis of the TBDMS ether protected ester **107** gave poor yields (30%) of the acid **108** even under mild conditions (1*N* LiOH in THF:H_2O) (Scheme 2.7)



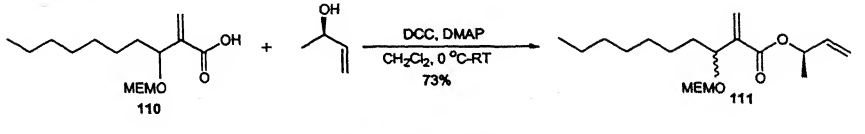
Scheme 2.7

All attempts to improve the yield of the acid product **108** using other reagents and conditions failed. So, we shifted our attention towards base stable protecting groups. Among the various protective groups tested, methoxy ethoxy methyl ether (MEM) was found to be the best. Thus, the treatment of hydroxy ester **106** with MEM-Cl in the presence of *N,N*-diisopropyl ethyl amine gave the MEM ether protected ester **109** in 83% yield which on hydrolysis with 1*N* LiOH in THF:H_2O mixture gave the desired acid **110** in a quantitative yield (Scheme 2.8).



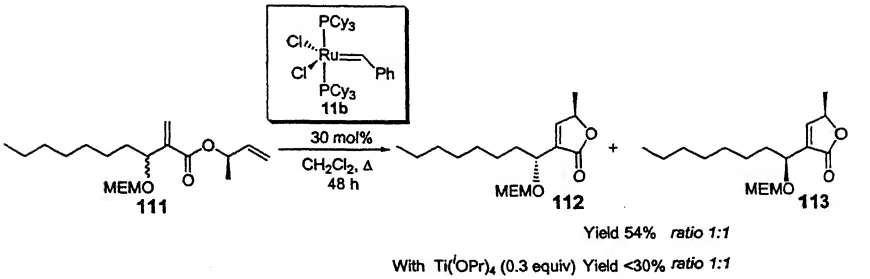
Scheme 2.8

The acid **110** was coupled with *R*-(-)-3-buten-2-ol in the presence of dicyclohexylcarbodiimide (DCC) and 4-(dimethylamino) pyridine (DMAP) to provide the diene ester **111** as an inseperable mixture of diastereomers, a substrate for ring closing metathesis reaction (Scheme 2.9).



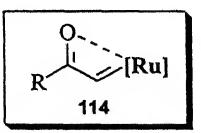
Scheme 2.9

Exposure of the diene ester **111** to a catalytic amount of the parent Grubbs catalyst **11b** in CH_2Cl_2 under high dilution conditions gave a diastereomeric mixture of cyclized products **112** and **113** in 54% yield (Scheme 2.10).



Scheme 2.10

Generally electron deficient olefins, such as acrylates, are known to be problematic substrates for RCM,[93] because the carbonyl group of the acrylate forms a stable chelate like **114**, with Ru carbene and deactivates its catalytic activity. This outcome, however, can be rectified upon addition of $Ti(O^iPr)_4$ to the reaction mixture.[94] Although the precise mode of action of $Ti(O^iPr)_4$ is not yet clear, it was believed that the oxophilic $Ti(O^iPr)_4$ competes with the emerging ruthenium carbene for a kinetically labile coordination onto the ester and, thereby, avoids the formation of unreactive intermediates such as chelate **114** (Figure 2.3).



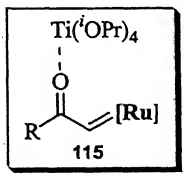
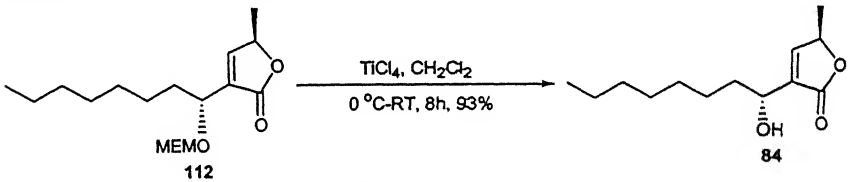


Figure 2.3

But in our case, the addition of substoichiometric amounts of $Ti(O^iPr)_4$ did not help in improving the yield of the cyclized products **112** and **113**. In fact, it decreased the yield to 30%. Although the reason was not clear, we believe that the presence of highly oxygenated MEM group also participates in coordination to Ti center and makes the molecule conformationally unfavorable for cyclization.

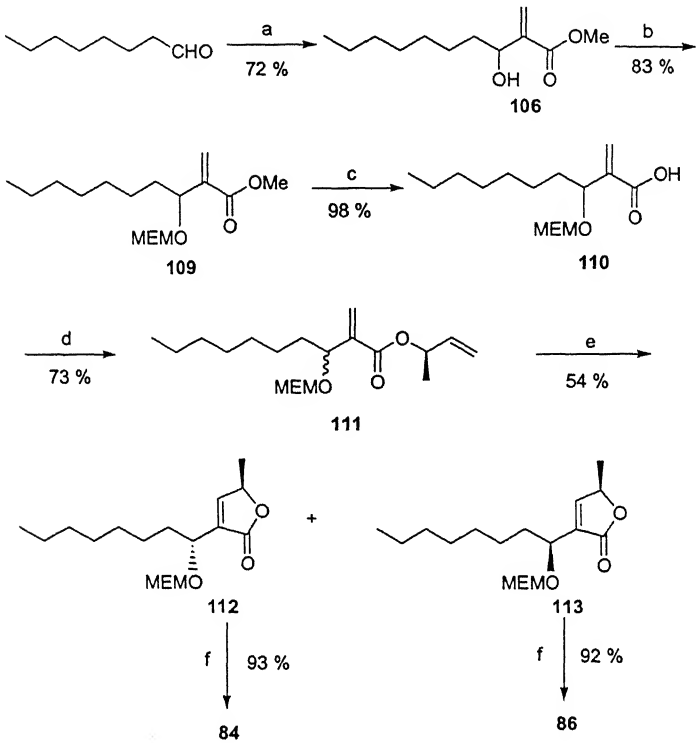
The diastereomers **112** and **113** were separated by radial chromatography and their absolute configurations were assigned after conversion to natural acaterin **84** and its diastereomer **86**. Thus, (-)-acaterin **84** was obtained in 93% yield after the deprotection of **112** with $TiCl_4$ (Scheme 2.11). By using similar procedure, pseudo acaterin **86** was obtained in 92% yield from **113**.



Scheme 2.11

We have accomplished the total synthesis of (-)-acaterin **84** along with one of its diastereomer **86** in an overall yield of 22% using ring-closing metathesis as a key step.[95] The overall scheme for the synthesis of (-)-acaterin **84** is presented in Scheme 2.12.

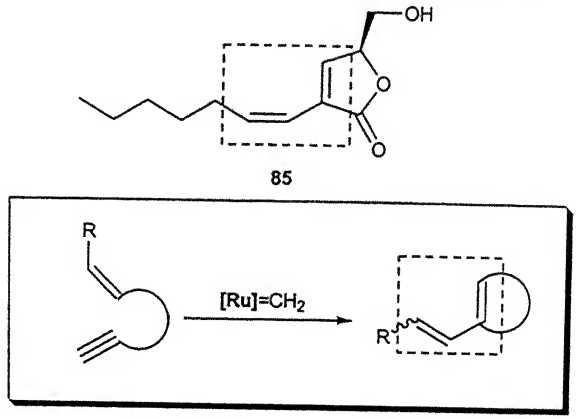
After successfully completing the synthesis of (-)-acaterin, we came across another interesting molecule (*S*)-fugomycin **85**, which is closely related to **84** both structurally and stereochemically.



conditions: (a) methyl acrylate, quinuclidine, RT, 48 h. (b) 2-methoxyethoxymethyl chloride, *N*-ethyl diisopropylamine, DCM, 0 °C-RT, 6 h. (c) 1*N* aq. LiOH, THF-water (2:1), 0 °C-RT, 24 h. (d) *R*-(-)- 3-buten-2-ol, DCC, DMAP, DCM, 0 °C-RT, 24 h. (e) Grubbs catalyst (30 mol%), DCM, reflux, 48 h. (f) $TiCl_4$, DCM, 0 °C-RT, 8 h.

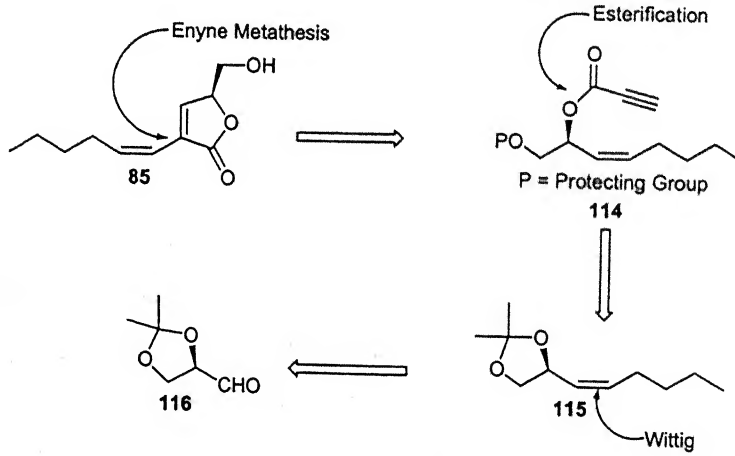
Scheme 2.12

(*S*)-Fugomycin, isolated from *Pseudomonas aureofaciens* with remarkable antifungal activity, is having a 1,3-butadiene skeleton in its structure.[86] Theoratically, the 5-membered ring of fugomycin along with butadiene skeleton can be constructed by using ring closing enyne metathesis (Scheme 2.13).



Scheme 2.13

Our retrosynthetic strategy towards synthesis of (*S*)-fugomycin **85**, based on enyne metathesis, is presented in Scheme 2.14.

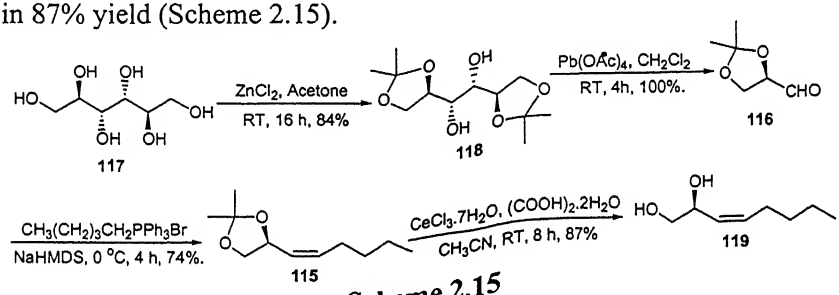


Scheme 2.14

A careful analysis of the target **85** reveals that the 5-membered ring of **85** can be constructed from enyne ester **114** by means of ring closing enyne metathesis. The enyne ester **114** could be obtained easily from acetonide derivative **115** through simple steps. The acetonide **115**

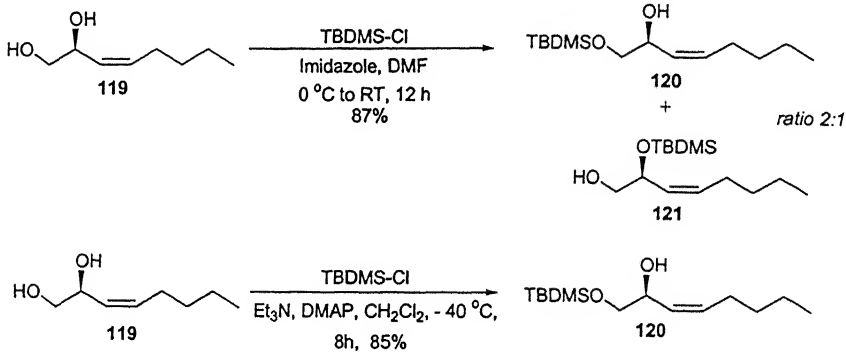
can be derived from (*R*)-1,2-isopropylidine glyceraldehyde, which in turn could be obtained from D-mannitol.

Thus, we started our synthesis from (*R*)-1,2-isopropylidine glyceraldehyde, which was derived from D-mannitol by literature known procedure.[96] The Wittig reaction of (*R*)-1,2-isopropylidine glyceraldehyde with pentyltriphenyl phosphonium bromide in the presence of NaHMDS gave exclusively the *cis* alkene **115** in 74% yield. Deprotection of the acetonide moiety of **115** with $CeCl_3.7H_2O$[97] in the presence of catalytic amount of oxalic acid provided the diol **119** in 87% yield (Scheme 2.15).



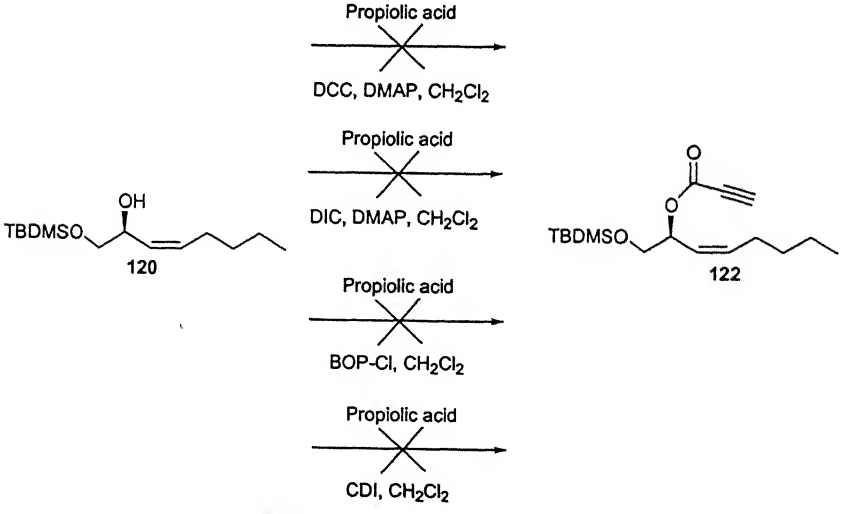
Scheme 2.15

We tried to protect the primary hydroxyl group of the diol **119** with TBDMS ether as the protecting group. The treatment of the diol **119** with TBDMS-Cl and imidazole in DMF gave an inseparable mixture of protected diols **120** and **121** in 2:1 ratio. However, a clean reaction was observed when we tried the same reaction with triethyl amine and DMAP in CH_2Cl_2 at –40 °C. Thus, the desired primary protected diol **120** was obtained in 85% yield (Scheme 2.16).



Scheme 2.16

Next step was the esterification of the allylic alcohol **120** with propiolic acid. Unfortunately, all attempts to synthesize the propargylate ester **122** under various reagents and conditions failed (Scheme 2.17). Further investigation to get the target ester **122** using other methods is currently under progress.



Scheme 2.17

In conclusion, we have developed a new route to the synthesis of (-)-acaterin **84** and one of its diastereomers **86** using RCM strategy. The overall yield of (-)-acaterin **84** and its diastereomer **86** by our method is 22%. We have also attempted the synthesis of (*S*)-fugomycin **85** using ring closing enyne metathesis strategy.

2.4. Experimental section:

General Methods and Materials:

^1H and ^{13}C NMR spectra were recorded on JEOL JNM-LA400 instrument using solutions in $CDCl_3$. The ^1H and ^{13}C spectra were referred, respectively, to TMS used as an internal standard and the central line for $CDCl_3$. Chemical shifts were reported in δ and coupling constants in Hz. IR spectra were recorded on Bruker FT IR Vector 22 spectrometer, samples are either in neat or KBr pellets. Optical rotations were taken on Rudolph Autopol-III automatic polarimeter. Elemental analyses were done on Perkin-Elmer 240-C automatic elemental analyzer. Mass spectrometric analyses were done on JEOL D-300 (EI/CI) and JEOL SX-102 (FAB) instruments. Melting points were determined by using Perfit apparatus and are uncorrected. The IUPAC names in the experimental section were generated using AutoNom software.

All the reactions were carried out using freshly distilled or dry solvents. Reagent grade solvents were obtained from S.D. Fine Chemicals Ltd. Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl under nitrogen. Dichloromethane, triethylamine, and chloroform were distilled over CaH_2. Routine monitoring of reactions were performed by tlc, using precoated silica gel tlc plates obtained from E-Merck. Column chromatography was performed over silica gel (100-200 mesh) from Acme Chemicals using petroleum ether and ethyl acetate mixtures as eluent. Solvents were removed under reduced pressure on a rotary evaporator. Organic extracts were dried

with anhydrous Na_2SO_4. The visualization of spots on tlc plates was effected by UV illumination, exposure to iodine vapor, DNP in 10% H_2SO_4 in ethanol and heating the plates sprayed with 10% H_2SO_4 in ethanol.

Methyl acrylate was distilled over a pinch of hydroquinone prier to use. Caprylic aldehyde, quinuclidine, DABCO, DCC, (*R*)-3-butene-2-ol, 2-methoxy ethoxymethylchloride, NaHMDS (2M solution), $CeCl_3.7H_2O$, TBDMS-Cl and Grubbs catalyst were obtained from Fluka and used as received.

3-Hydroxy-2-methylene-decanoic acid methyl ester 106. A solution of caprylic aldehyde (3.0 mL, 19.2 mmol) and freshly distilled methyl acrylate (10 mL) was stirred in the presence of quinuclidine (500 mg, 4.5 mmol) at room temperature for 48 h. Most of the methyl acrylate was distilled off under reduced pressure and the residue was chromatographed over silica gel using 10% EtOAc in petroleum ether (ratio 1:9) to provide **106** as a colorless oil; Yield 2.95 g (72%); R_f 0.30 (10% ethyl acetate in petroleum ether); FT IR (film) 3443 (br), 1716, 1631 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.87 (t, J = 6.7 Hz, 3H), 1.27-1.35 (m, 10H), 1.60-1.68 (m, 2H), 2.55 (bs, 1H), 3.79 (s, 3H), 4.38 (bt, J = 6.4 Hz, 1H), 5.79 (t, J = 1.2 Hz, 1H), 6.22 (d, J = 0.72 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.06, 22.62, 25.82, 29.20, 29.36, 31.78, 36.20, 51.84, 71.83, 124.93, 142.45, 167.05; Mass (EI, *m/z*): 214 (M^+). Anal. Calcd. for $C_{12}H_{22}O_3$: C, 67.29; H, 10.28. Found: C, 67.27; H, 10.30.

3-(2-Methoxy-ethoxymethoxy)-2-methylene-decanoic acid methyl ester 109. A solution of the adduct **106** (2.0 g, 9.4 mmol) and *N*-ethyl diisopropylamine (3.2 mL, 18.7 mmol) in *anhydrous* CH_2Cl_2 (20 mL) was treated with 2-methoxy ethoxymethyl chloride (1.6 mL, 14.0 mmol) at room temperature for 6 h. The reaction mixture was then filtered through a pad of celite, diluted with CH_2Cl_2 and washed with 0.1 *N* HCl, water, saturated brine solution and dried over *anhydrous* Na_2SO_4. The solvent was removed under reduced pressure and the residue was purified through silica gel column using 5% EtOAc in petroleum ether to give the MEM ester **109** as a colorless oil; Yield 2.34 g (83%). R_f 0.5 (15% ethyl acetate in petroleum ether); FT IR (film) 1722, 1631 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.87 (t, J = 7.1 Hz, 3H), 1.26–1.35 (m, 10H), 1.53–1.62 (m, 1H), 1.64–1.69 (m, 1H), 3.39 (s, 3H), 3.53–3.56 (m, 2H), 3.60–3.66 (m, 1H), 3.76 (s, 3H), 3.77–3.82 (m, 1H), 4.52 (bdd, J = 7.8, 4.4 Hz, 1H), 4.67 (s, 2H), 5.82 (t, J = 1.2 Hz, 1H), 6.28 (d, J = 1.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.05, 22.60, 25.56, 29.18, 29.32, 31.78, 35.63, 51.75, 58.98, 67.19, 71.68, 74.64, 93.73, 125.32, 141.20, 166.53; ; Mass (EI, *m/z*): 213, 197, 105, 89 (base peak). Anal. Calcd. for $C_{16}H_{30}O_5$: C, 63.58; H, 9.93. Found: C, 63.60; H, 9.91.

3-(2-Methoxy-ethoxymethoxy)-2-methylene-decanoic acid 110. A solution of *aqueous* 1*N* LiOH (66.2 mL, 66.2 mmol) was added drop-wise to a stirred solution of methyl ester **109** (2.0 g, 6.6 mmol) in THF (100 mL) and water (50 mL) at 0 °C. The cooling bath was then removed and the mixture was stirred at room temperature. On

completion of the reaction (*ca.* 24 h), the reaction mixture was acidified to pH 4 with dilute *aqueous* HCl at 0 °C and extracted with EtOAc. The organic layer was then washed with saturated brine solution, dried over *anhydrous* Na_2SO_4. Evaporation of the solvent followed by purification over silica gel column using 50% EtOAc in petroleum ether gave the acid **110** as a colorless oil. Yield 1.88 g (98 %). R_f 0.50 (neat EtOAc); FT IR (film) 3300-2500, 1717, 1632 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.80 (t, J = 6.6 Hz, 3H), 1.18-1.26 (m, 10H), 1.49-1.65 (m, 2H), 3.32 (s, 3H), 3.49 (t, J = 4.8 Hz, 2H), 3.55-3.60 (m, 1H), 3.71-3.76 (m, 1H), 4.45 (bdd, J = 7.6, 4.4 Hz, 1H), 4.62 (s, 2H), 5.86 (s, 1H), 6.35 (d, J = 1.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.03, 22.59, 25.56, 29.18, 29.31, 31.78, 35.52, 58.95, 67.22, 71.64, 74.61, 93.76, 127.57, 140.72, 170.83; Mass (FAB, m/z): 184, 106, 90 (base peak). Anal. Calcd. for $C_{15}H_{28}O_5$: C, 62.50; H, 9.72. Found: C, 62.44; H 9.75.

3-(*RS*)-(2-Methoxy-ethoxymethoxy)-2-methylene-decanoic acid-(1*R*)-methyl-allyl ester 111. A solution of DCC (2.13 g, 10.34 mmol) in *anhydrous* CH_2Cl_2 (5 mL) was added drop-wise to a solution of the acid **110** (1.5 g, 5.2 mmol), *R*-(-)-3-buten-2-ol (536 µL, 6.2 mmol) and DMAP (316 mg, 2.6 mmol) in *anhydrous* CH_2Cl_2 (15 mL) at 0 °C. The reaction mixture was slowly warmed to room temperature and allowed to stir for 24 h. It was filtered through a pad of celite, diluted with CH_2Cl_2, washed with water, saturated brine, and dried over *anhydrous* Na_2SO_4. Evaporation of the solvent followed by purification over silica gel column using 10% EtOAc in petroleum ether provided an inseparable diastereomeric mixture of products **111** as a colorless oil;

Yield 1.30 g (73 %); R_f 0.65 (20% EtOAc in petroleum ether); $[\alpha]^{25}_D$ 3.48 (*c* 1.15, $CHCl_3$); IR (film) 1713, 1632 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.80 (t, J = 6.6 Hz, 3H), 1.19-1.21 (m, 10H), 1.28 (dd, J = 6.4, 2.0 Hz, 3H), 1.50-1.64 (m, 2H), 3.32 (s, 3H), 3.46-3.49 (m, 2H), 3.54-3.59 (m, 1H), 3.70-3.76 (m, 1H), 4.46 (bm, 1H), 4.60 (s, 2H), 5.08 (qd, J = 10.5, 1.2 Hz, 1H), 5.19 (tdd, J = 17.3, 2.2, 1.2, Hz, 1H), 5.31-5.38 (m, 1H), 5.74 (d, J = 1.2 Hz, 1H), 5.75-5.85 (m, 1H), 6.22 (d, J = 1.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.07, 19.89, 22.63, 25.61, 29.22, 29.35, 29.68, 31.81, 35.78, 59.01, 67.22, 71.29, 71.36, 71.72, 74.66, 74.73, 93.83, 115.77, 115.89, 124.87, 124.92, 137.54, 141.72, 165.29 (Most of the carbons showed two peaks due to the presence of diastereomers); Mass (EI, *m/z*): 237, 105, 89 (base peak). Anal. Calcd. for $C_{19}H_{34}O_5$: C, 66.67; H, 9.94. Found: C, 66.55; H, 9.98.

Cyclization of diene 111. A solution of Grubbs carbene (358 mg, 0.44 mmol) in *anhydrous* CH_2Cl_2 (100 mL) was added drop-wise to a stirred solution of the diene **111** (500 mg, 1.45 mmol) in *anhydrous* CH_2Cl_2 (100 mL) at 40 °C over a period of 1.5 h. The resulting solution was allowed to stir at reflux temperature for 48 h. The solvent was distilled off under reduced pressure and the residue was passed through a short plug of silica gel to give a 1:1 diastereomeric mixture of products **112** and **113** as a pale brown coloured liquid; Yield 246 mg (54 %). These diastereomers were separated by a radial chromatography using 1-2 mm thick plates coated with silica gel PF_{254} (E-Merck) to give **112** (116 mg) and **113** (110 mg).

2-[1*R*-(Methoxy-ethoxymethoxy)-octyl]-4*R*-pent-2-enolide 112. R_f 0.48 (50% EtOAc in petroleum ether); $[\alpha]^{25}_D$ +21.9 (*c* 0.60, $CHCl_3$); IR (film) 1753 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.87 (t, J = 6.4 Hz, 3H), 1.26-1.29 (m, 10H), 1.43 (d, J = 6.8 Hz, 3H), 1.71-1.78 (m, 2H), 3.38 (s, 3H), 3.54 (t, J = 4.9 Hz, 2H), 3.64-3.69 (m, 1H), 3.73-3.78 (m, 1H), 4.48 (bt, J = 6.1 Hz, 1H), 4.73 (d, J = 2.4 Hz, 2H), 5.04 (q, J = 6.8 Hz, 1H), 7.26 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.07, 19.08, 22.61, 25.05, 29.18, 29.32, 31.77, 33.89, 59.06, 67.37, 71.54, 71.66, 77.58, 94.10, 134.88, 150.71, 171.84. Mass (EI, *m/z*): 269 (base peak). Anal. Calcd. for $C_{17}H_{30}O_5$: C, 64.97; H, 9.95. Found: C, 64.84; H, 9.97.

2-[1*S*-(Methoxy ethoxymethoxy)-octyl]-4*R*-pent-2-enolide 113. R_f 0.5 (50% EtOAc in petroleum ether); $[\alpha]^{25}_D$ –82.4 (*c* 0.85, $CHCl_3$); IR (film) 1755 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.87 (t, J = 6.6 Hz, 3H), 1.26-1.29 (m, 10H), 1.43 (d, J = 6.8 Hz, 3H), 1.72-1.80 (m, 2H), 3.39 (s, 3H), 3.54 (t, J = 4.9 Hz, 2H), 3.64-3.69 (m, 1H), 3.74-3.79 (m, 1H), 4.48 (t, J = 6.3 Hz, 1H), 4.73 (s, 2H), 5.05 (q, J = 6.8 Hz, 1H), 7.22 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.06, 19.11, 22.60, 25.13, 29.18, 29.32, 31.78, 33.92, 59.05, 67.36, 71.55, 71.66, 77.58, 94.12, 134.85, 150.67, 171.86. Anal. Calcd. for $C_{17}H_{30}O_5$: C, 64.97; H, 9.95. Found: C, 64.94; H, 9.92.

Natural (-)-acaterin 84. A solution of $TiCl_4$ (174 µL, 1.58 mmol) in *anhydrous* CH_2Cl_2 (2 mL) was added drop-wise to a stirred solution of **112** (50 mg, 0.16 mmol) in *anhydrous* CH_2Cl_2 (2 mL) at 0 °C. After being stirred for 12 h at rt, the reaction mixture was quenched with concentrated NH_4OH at 0 °C and extracted with CH_2Cl_2. The combined

organic layer was washed with saturated brine solution, dried over *anhydrous* Na_2SO_4. Evaporation of the solvent under *vacuo* gave crude material, which on purification over silica gel column using 30% EtOAc in petroleum ether gave the natural acaterin **84** as a colorless oil. Yield 34 mg (93 %). R_f 0.40 (50% EtOAc in petroleum ether); $[\alpha]^{25}_D$ –18.9 (*c* 0.95, $CHCl_3$) {lit.[78] $[\alpha]^{19}_D$ –17 ($CHCl_3$); lit.[82a] $[\alpha]^{20}_D$ -19.7 (*c* 0.61, $CHCl_3$)}; IR (film) 3458, 1750, 1652 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.88 (t, J = 7.1 Hz, 3H), 1.27-1.30 (m, 10H), 1.45 (d, J = 6.8 Hz, 3H), 1.64-1.81 (m, 2H), 2.69 (bs, 1H), 4.47-4.50 (m, 1H), 5.07 (q, J = 6.8 Hz, 1H), 7.19 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.05, 18.90, 22.59, 25.23, 29.15, 29.28, 31.73, 35.41, 66.99, 77.95, 136.15, 149.32, 172.67.

***Pseudo* acaterin 86.** The above-described procedure was followed for the conversion of **113** into **86**. The product **86** was obtained as a colorless oil. Yield 33 mg (92 %); R_f 0.42 (50% EtOAc in petroleum ether); $[\alpha]^{25}_D$ –54.7 (*c* 0.75 in $CHCl_3$) {lit.[82a] $[\alpha]^{25}_D$ –63.7 (*c* 0.53, $CHCl_3$)} ; IR (film) 3458, 1750, 1652 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.88 (t, J = 7.1 Hz, 3H), 1.27-1.32 (m, 10H), 1.44 (d, J = 6.8 Hz, 3H), 1.66-1.81 (m, 2H), 2.62 (bs, 1H), 4.49 (m, 1H), 5.07 (q, J = 6.8 Hz, 1H), 7.19 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.05, 18.93, 22.59, 25.28, 29.16, 29.28, 31.74, 35.43, 67.08, 77.95, 136.21, 149.28, 172.63.

(3*R*)-4-Hept-1-enyl-2,2-dimethyl-[1,3]dioxolane 115: NaHMDS (2 M solution in THF) (16.2 mL, 32.4 mmol) was added drop-wise to a stirred suspension of *n*-pentyl triphenylphosphonium bromide [prepared

by heating 1-bromopentane and triphenylphosphine in *anhydrous* benzene for 24 h] (12.8 g, 30.0 mmol) in *anhydrous* THF (70 mL) at 0 °C. The resulting bright orange mixture was further stirred at 0 °C for 30 min. A solution of (*R*)-1,2-isopropylidine glyceraldehyde[96] **116** (3.0 g, 23.1 mmol) in *anhydrous* THF (30 mL) was added drop-wise to it. After being stirred for 4 h at 0 °C, the reaction mixture was quenched with saturated *aqueous* NH_4Cl solution. The organic layer was separated and the aqueous layer was extracted with ether. The combined organic layer was washed with saturated brine solution and dried over *anhydrous* Na_2SO_4. The solvent was evaporated in *vacuo* and the crude material on purification over silicagel column using 1% EtOAc in petroleum ether gave the pure compound **115** as a colorless oil. Yield 3.16 g (74 %); R_f 0.80 (5% EtOAc in petroleum ether); $[\alpha]^{25}_D$ +7.0 (*c* 1, $CDCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90 (t, J = 7.2 Hz, 3H), 1.25-1.36 (m, 4H), 1.40 (d, J = 0.4 Hz, 3H), 1.42 (d, J = 0.5 Hz, 3H), 2.05-2.17 (m, 2H), 3.51 (t, J = 8.0 Hz, 1H), 4.06 (dd, J = 8.0, 5.8 Hz, 1H), 4.84 (ddt, J = 8.6, 6.1, 1.2 Hz, 1H), 5.40 (tdd, J = 12.4, 8.6, 1.5 Hz, 1H), 5.63 (dtd, J = 11.0, 7.6, 1.2 Hz, 1H); ^{13}C NMR (100 MHz $CDCl_3$) δ 13.86, 21.20, 25.98, 26.76, 27.43, 31.75, 69.45, 71.98, 109.00, 126.98, 135.17; MS (FAB): 185 (M^++1). Anal. Calcd. for $C_{11}H_{20}O_2$: C, 71.74; H, 10.87. Found: C, 71.67; H, 10.48.

(*2R*)-Non-3-ene-1,2-diol 119: $CeCl_3.7H_2O$ (12.2 g, 32.6 mmol) was added, in portions, to a solution of acetonide **115** (3.0 g, 16.3 mmol) in acetonitrile (100 mL) followed by $(COOH)_2.2H_2O$ (103 mg, 0.82 mmol) at rt. After being stirred for 4 h, the reaction mixture was filtered

and washed with acetonitrile. The filtrate was evaporated to dryness using rotary evaporator and the residue on purification over silica gel column using 50% EtOAc in petroleum ether gave pure diol **119** as a colorless oil. Yield 2.04 g (87%); R_f 0.50 (70% EtOAc in petroleum ether); $[\alpha]^{25}_D$ +9.2 (*c* 1.4, $CHCl_3$); FT IR (neat) 3438 (br) cm^{-1}: ^1H NMR (400 MHz, $CDCl_3$) δ 0.90 (t, J = 7.1 Hz, 3H), 1.27-1.37 (m, 4H), 2.00-2.16 (m, 2H), 2.82 (bs, 2H), 3.48 (dd, J = 11.2, 8.1 Hz, 1H), 3.57 (dd, J = 11.5, 3.7 Hz, 1H), 4.55 (ddt, J = 8.5, 3.7, 1.0 Hz, 1H) 5.36 (tdd, J = 11.0, 8.7, 1.5 Hz, 1H), 5.58 (dtd, J = 11.0, 7.6, 1.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.88, 22.27, 27.59, 31.72, 66.32, 68.62, 127.68, 134.52; MS (FAB): 167 (M^++ Na). Anal. Calcd. for $C_8H_{16}O_2$: C, 66.67; H, 11.11. Found: C, 66.48; H, 11.09.

(2*R*)-1-(*tert*-Butyl-dimethyl-silanyloxy)-oct-3-en-2-ol 120: A solution of TBDMS-Cl (1.97 g, 13.1 mmol) in *anhydrous* CH_2Cl_2 (10 mL) was added drop-wise to a stirred solution of diol **119** (1.8 g, 12.5 mmol), Et_3N (5.2 mL, 37.5 mmol) and 4-DMAP (153 mg, 1.25 mmol) in *anhydrous* CH_2Cl_2 (60 mL) at – 40 °C. After being stirred for 8 h at the same temperature, the reaction mixture was diluted with CH_2Cl_2, washed with water and saturated brine solution and dried over *anhydrous* Na_2SO_4. The solvent was evaporated under *vacuo* and the residue on purification over silicagel column using 2% EtOAc in petroleum ether gave the pure compound **120** as a colorless oil. Yield 2.74 g (85%). R_f 0.6 (10% EtOAc in petroleum ether); $[\alpha]^{25}_D$ +35.8 (*c* 1.35, $CDCl_3$); FT IR (neat) 3449 (br) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.00 (s, 6H), 0.82 (m, 3H [CH_3 signal was merged with ^{t}Bu methyl

signal]), 0.83 (s, 3H), 1.22-1.28 (bm, 4H), 1.93-2.08 (m, 2H), 2.46 (bs, 1H), 3.33 (dd, J = 10.0, 8.32 Hz, 1H), 3.48 (dd, J = 10.0, 3.64 Hz, 1H), 4.39 (dt, J = 8.28, 2.92 Hz, 1H), 5.21-5.26 (m, 1H), 5.48 (dtd, J = 11.0, 7.56, 0.96 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ –5.40, -5.32, 13.91, 18.31, 22.28, 25.88, 27.65, 31.82, 66.87, 68.36, 127.66, 134.31. Anal. Calcd. for $C_{14}H_{30}O_2Si$: C, 65.15; H, 11.63. Found: C, 65.43; H, 11.28.

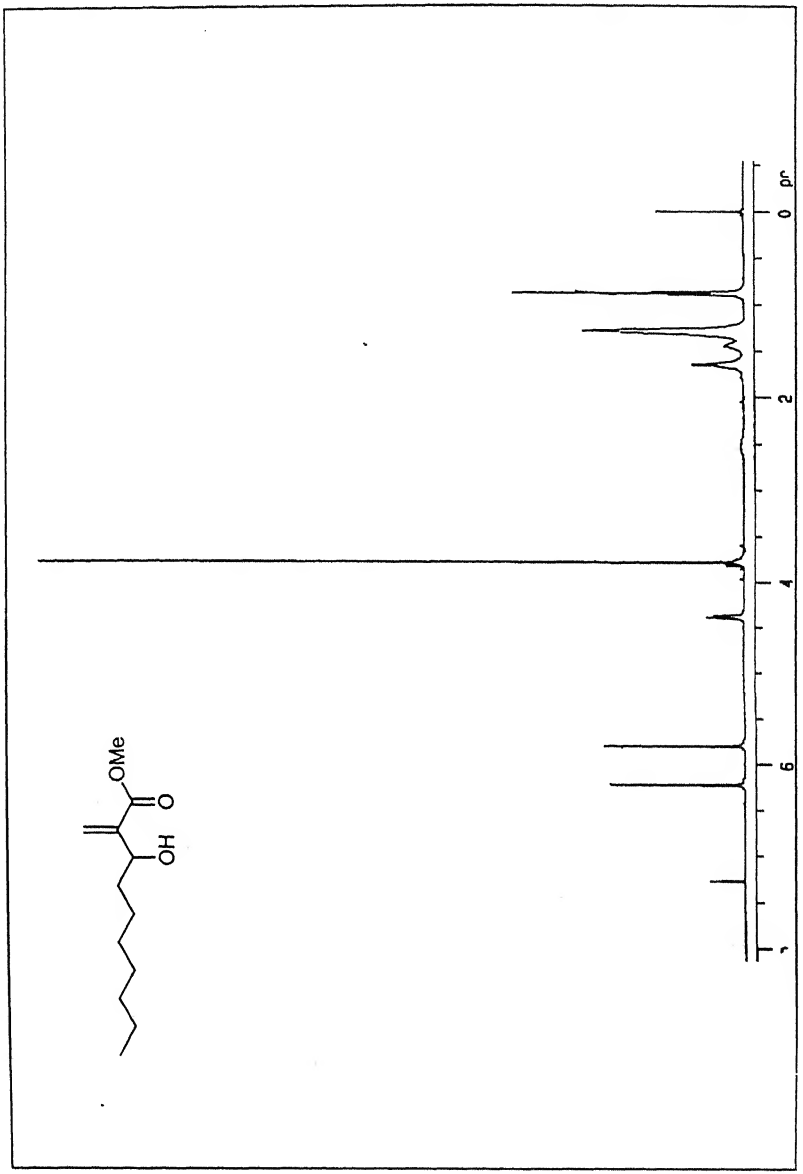


Figure 2.1 ^{1}H NMR of **106**

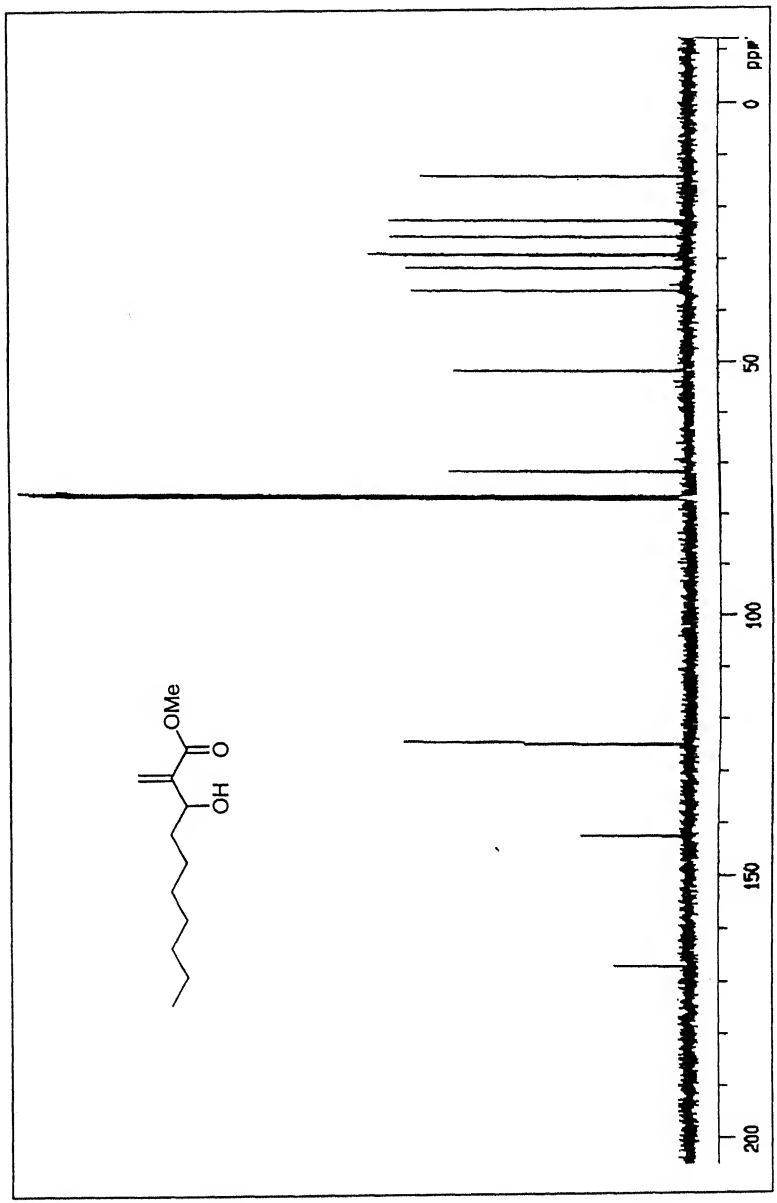


Figure 2.2 ^{13}C NMR of 106

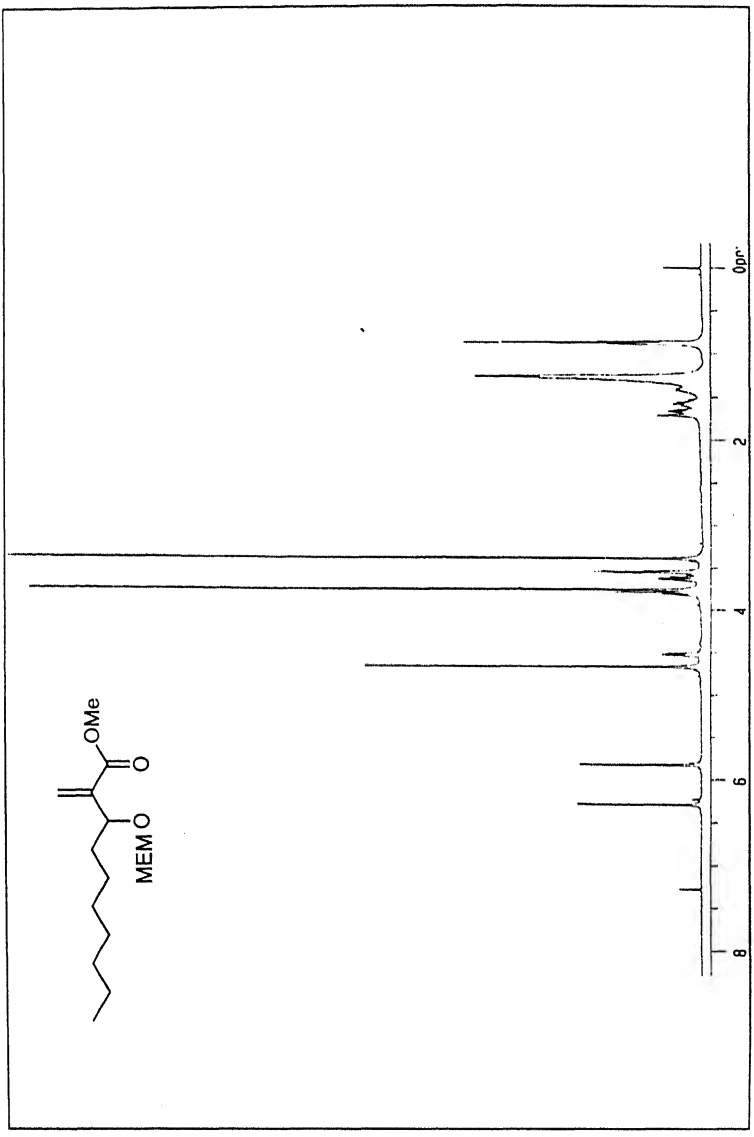


Figure 2.3 ^{1}H NMR of **109**

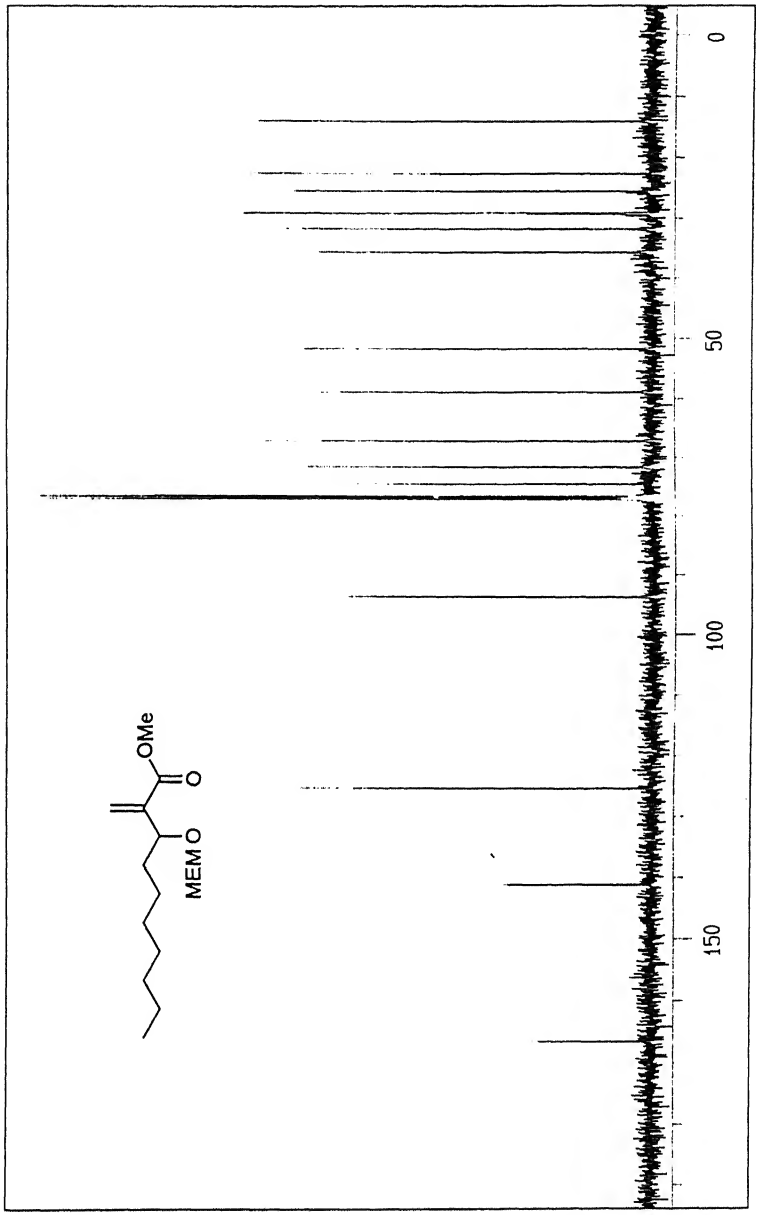


Figure 2.4 ^{13}C NMR of **109**

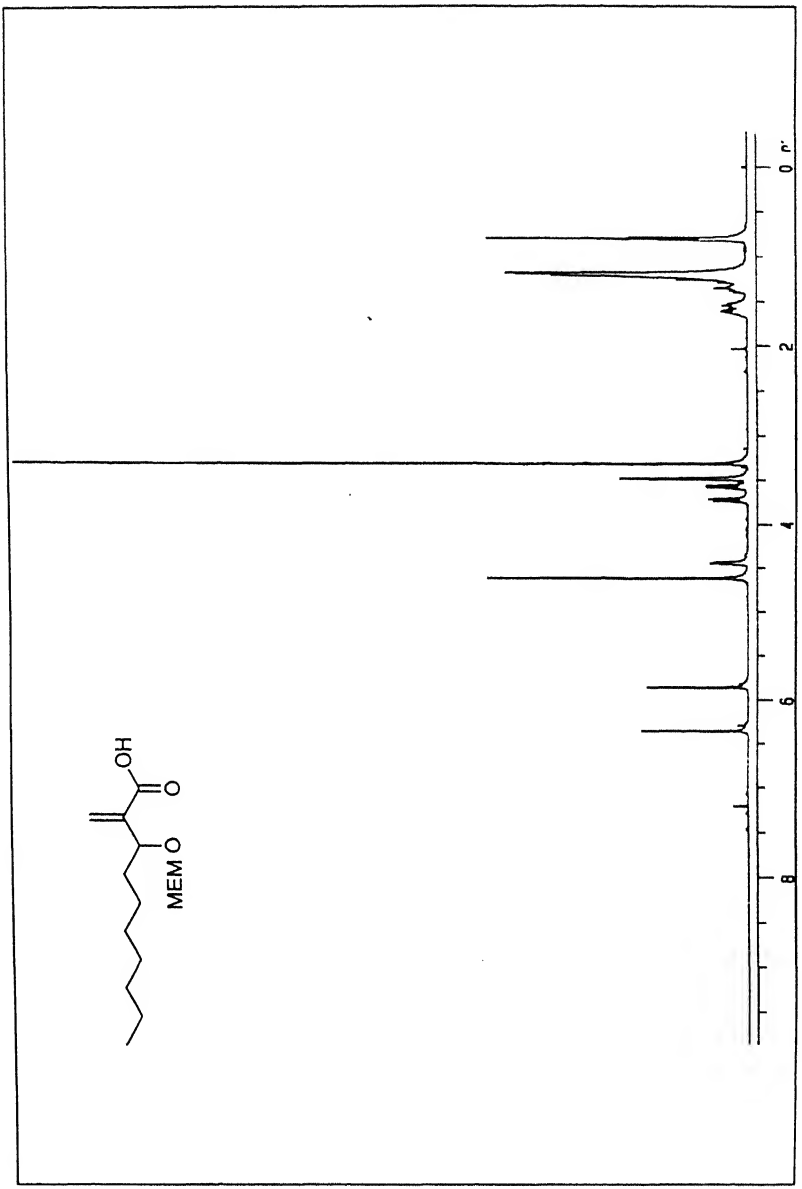


Figure 2.5 ^{1}H NMR of **110**

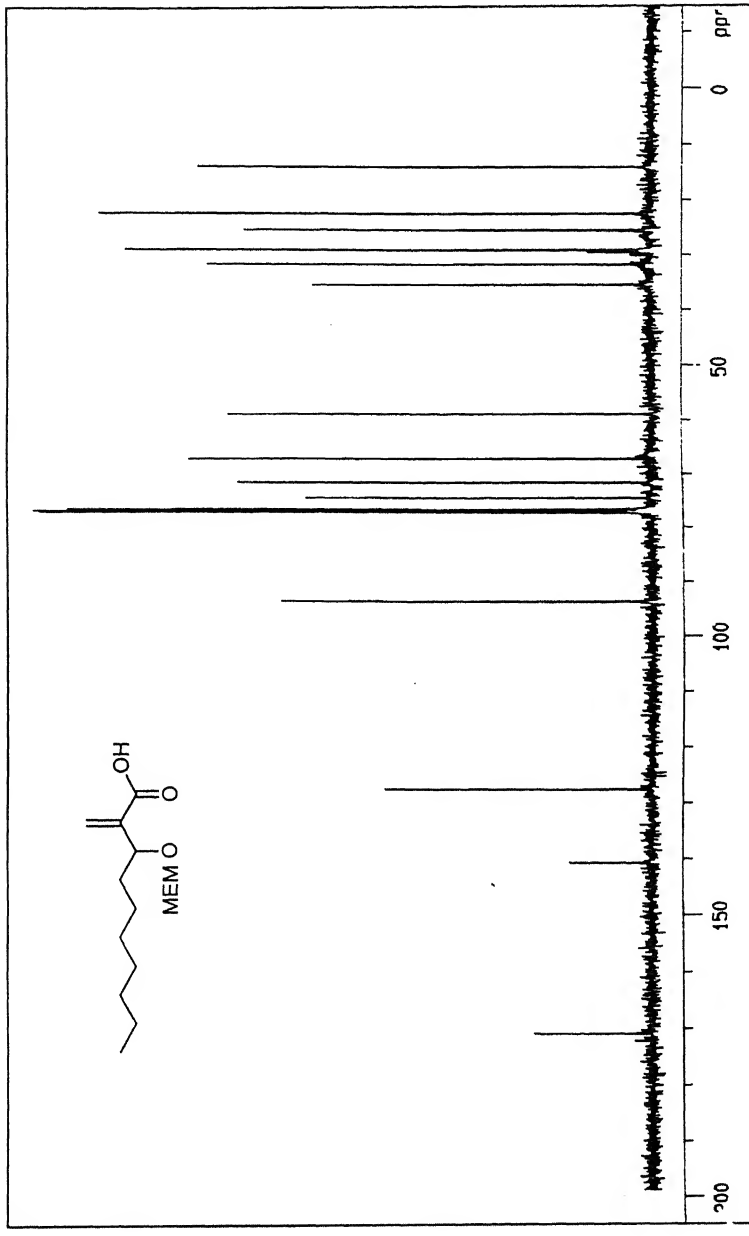


Figure 2.6 ^{13}C NMR of **110**

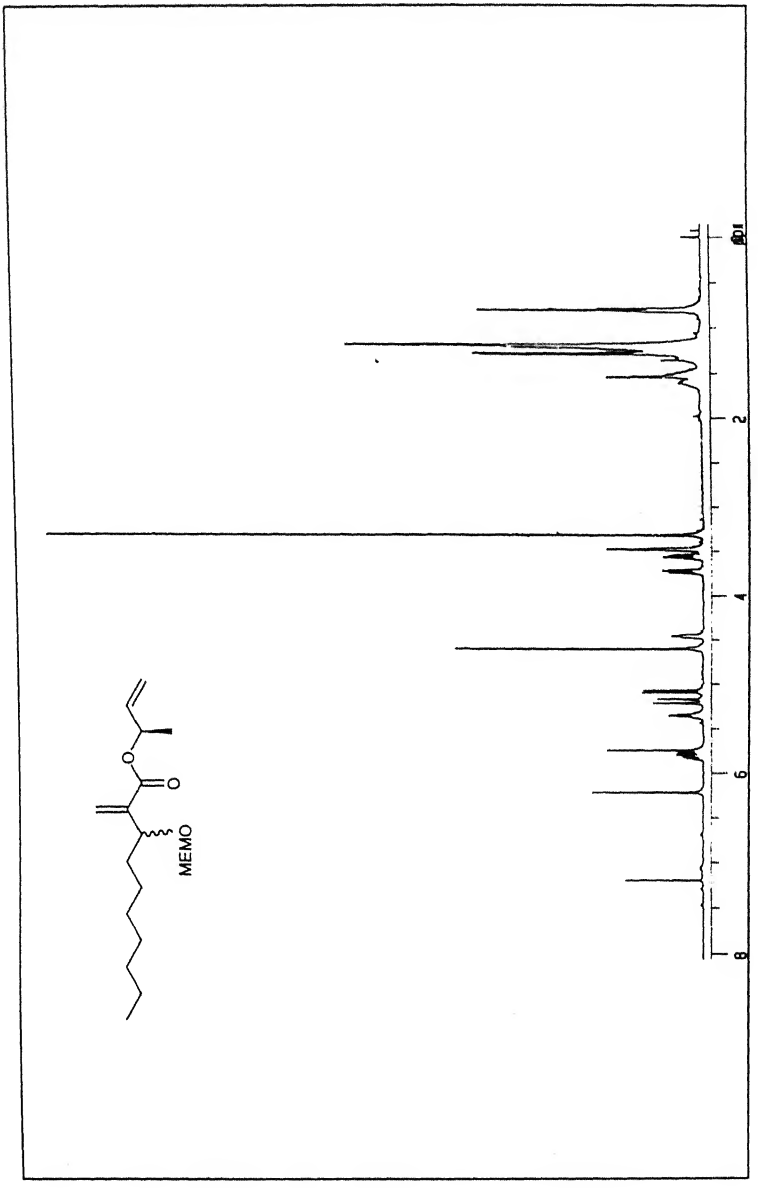


Figure 2.7 ^{1}H NMR of **111**

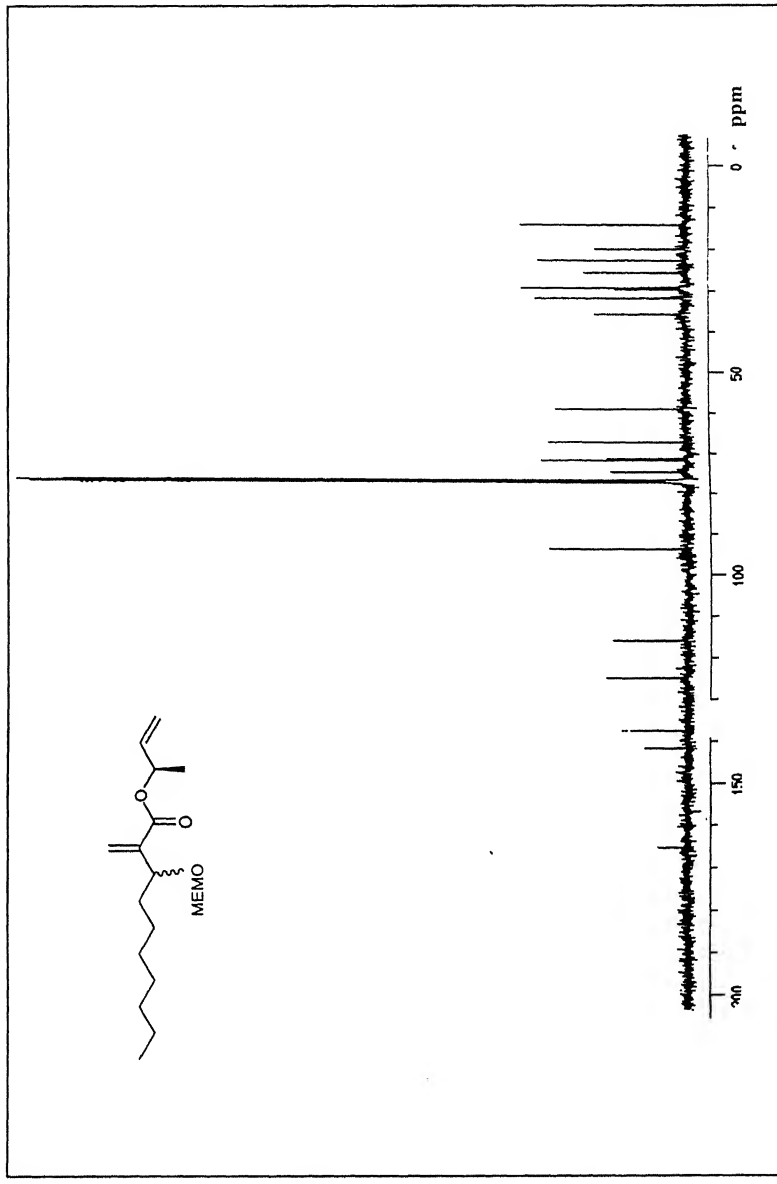


Figure 2.8 ^{13}C NMR of **111**

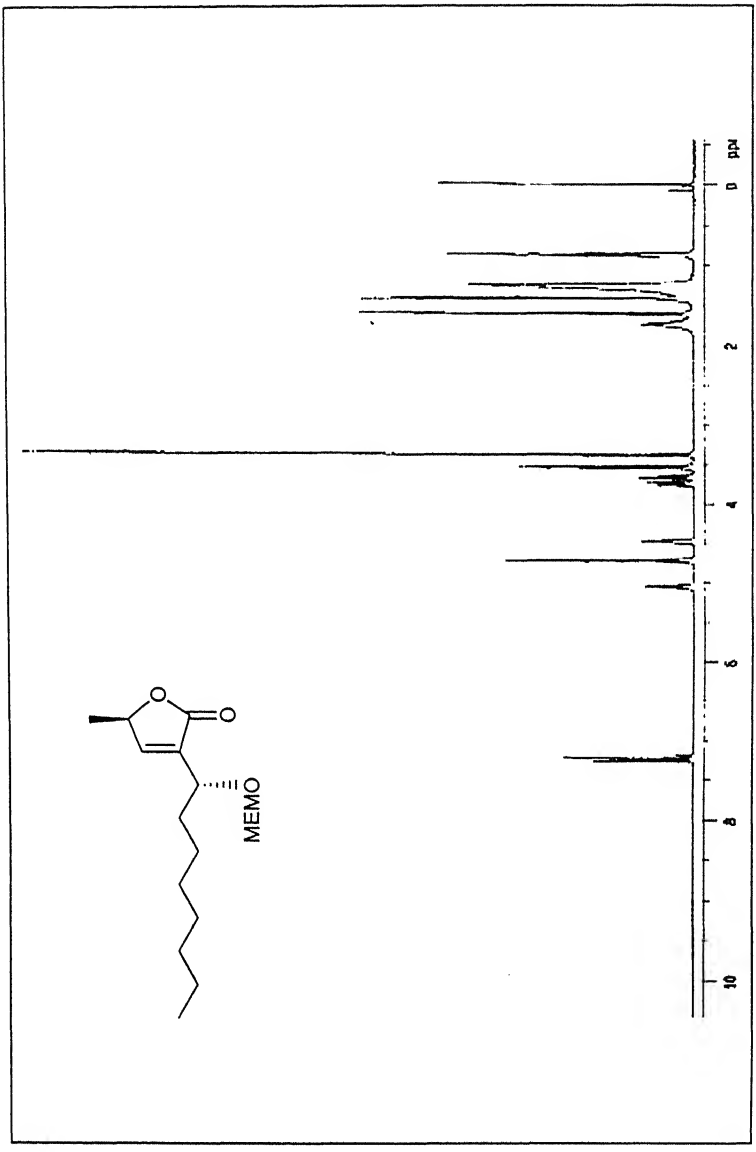


Figure 2.9 ^{1}H NMR of **112**

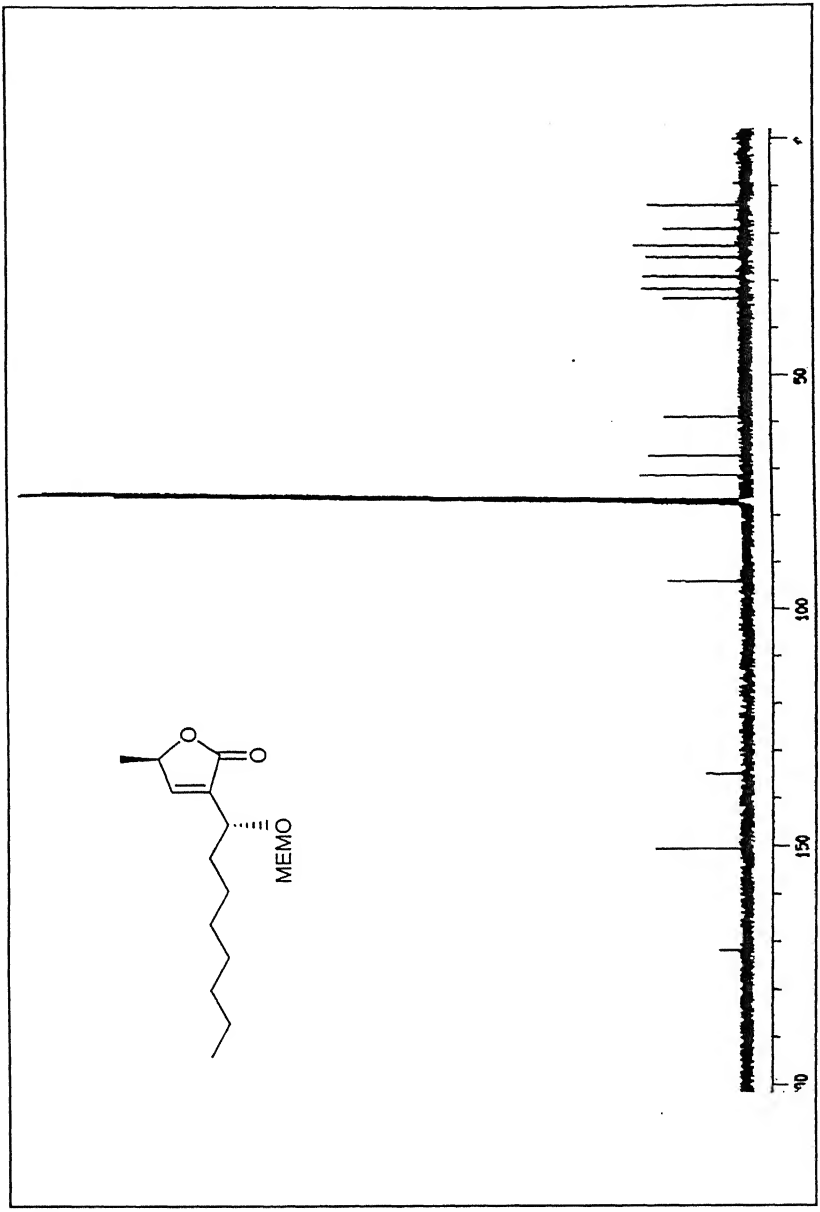


Figure 2.10 ^{13}C NMR of **112**

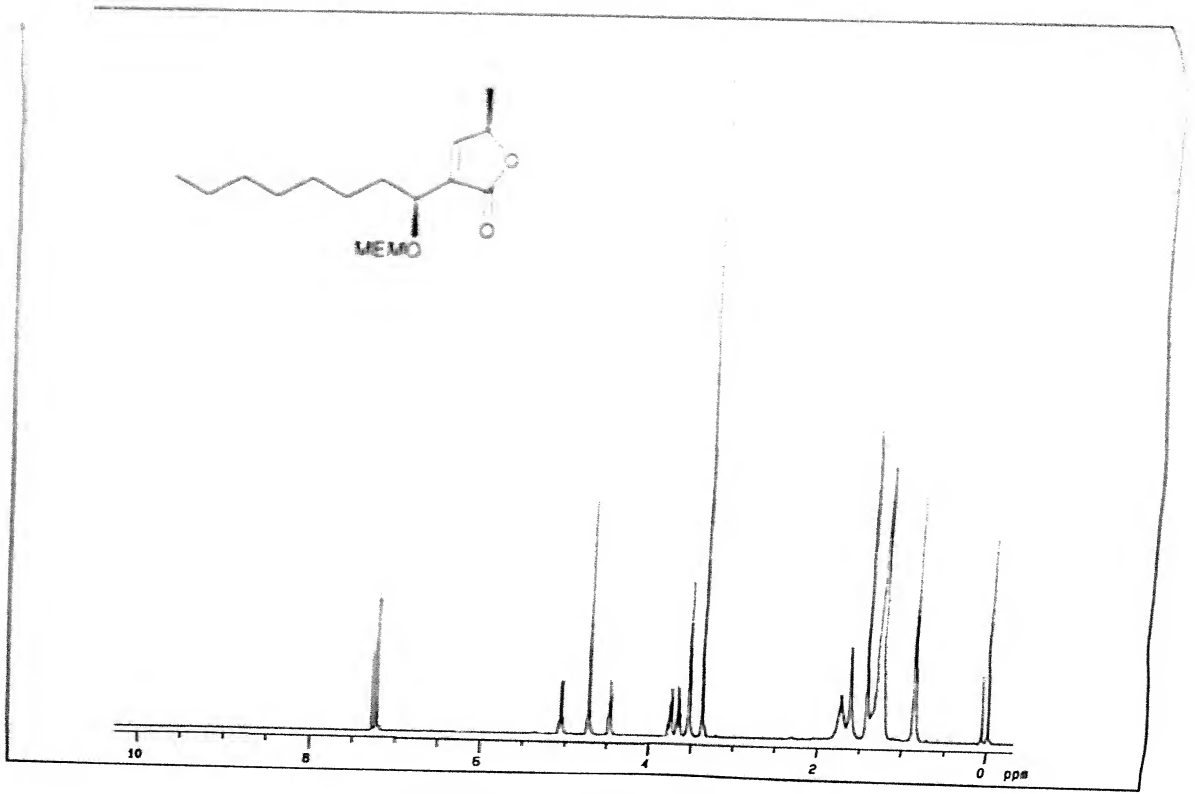


Figure 2.11 ^{1}H NMR of **113**

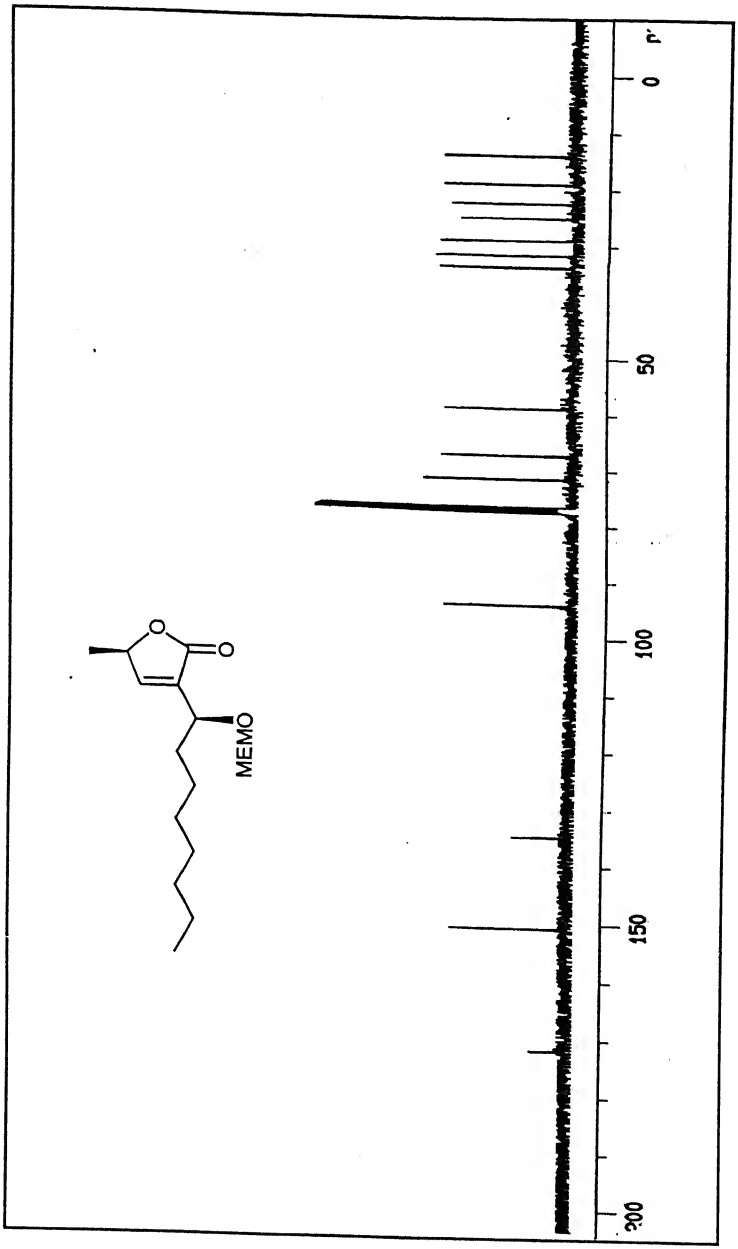


Figure 2.12 ^{13}C NMR of **113**

Figure 2.13 ^{1}H NMR of **84**

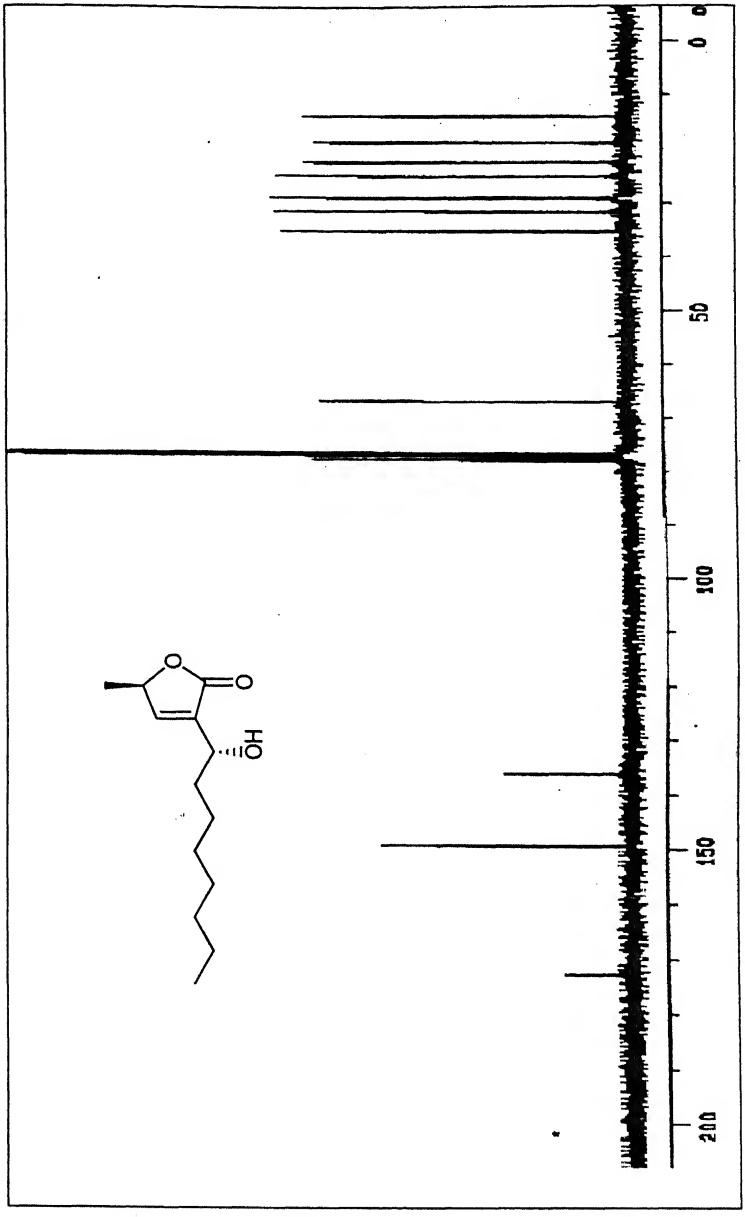


Figure 2.14 ^{13}C NMR of **84**

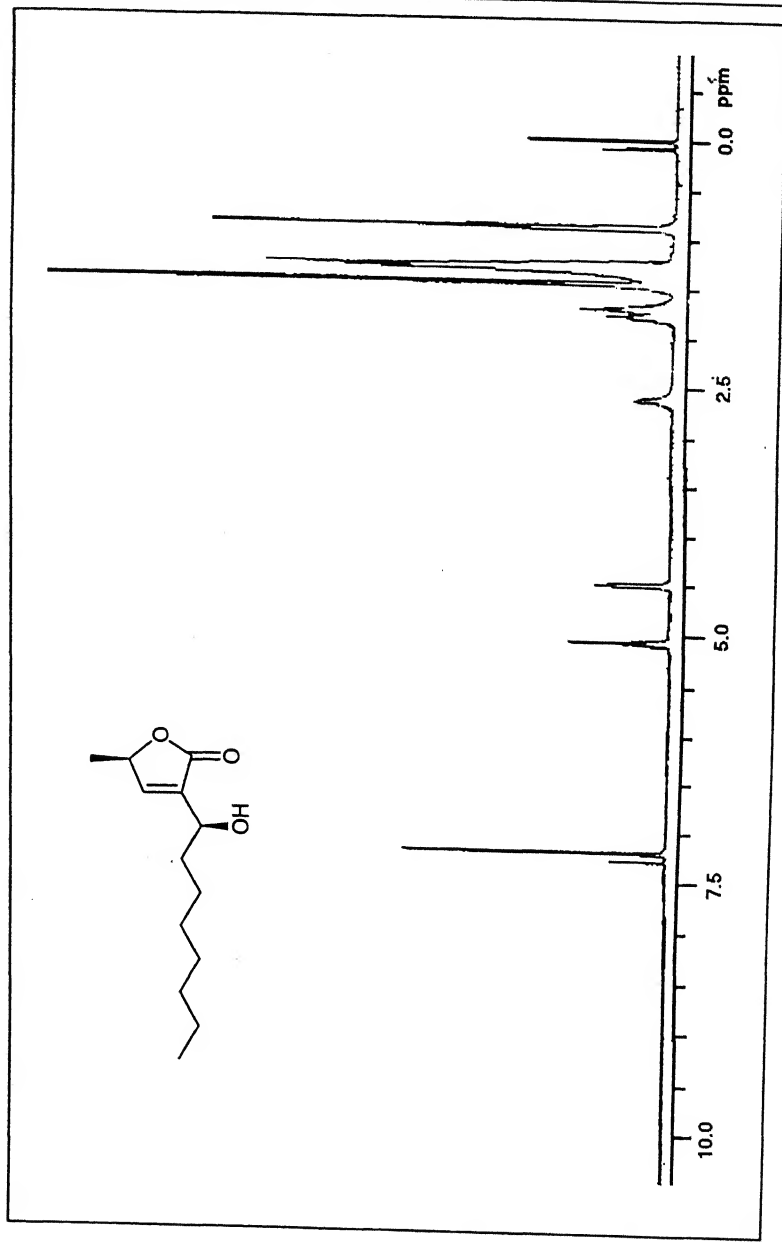


Figure 2.15 ^{1}H NMR of **86**

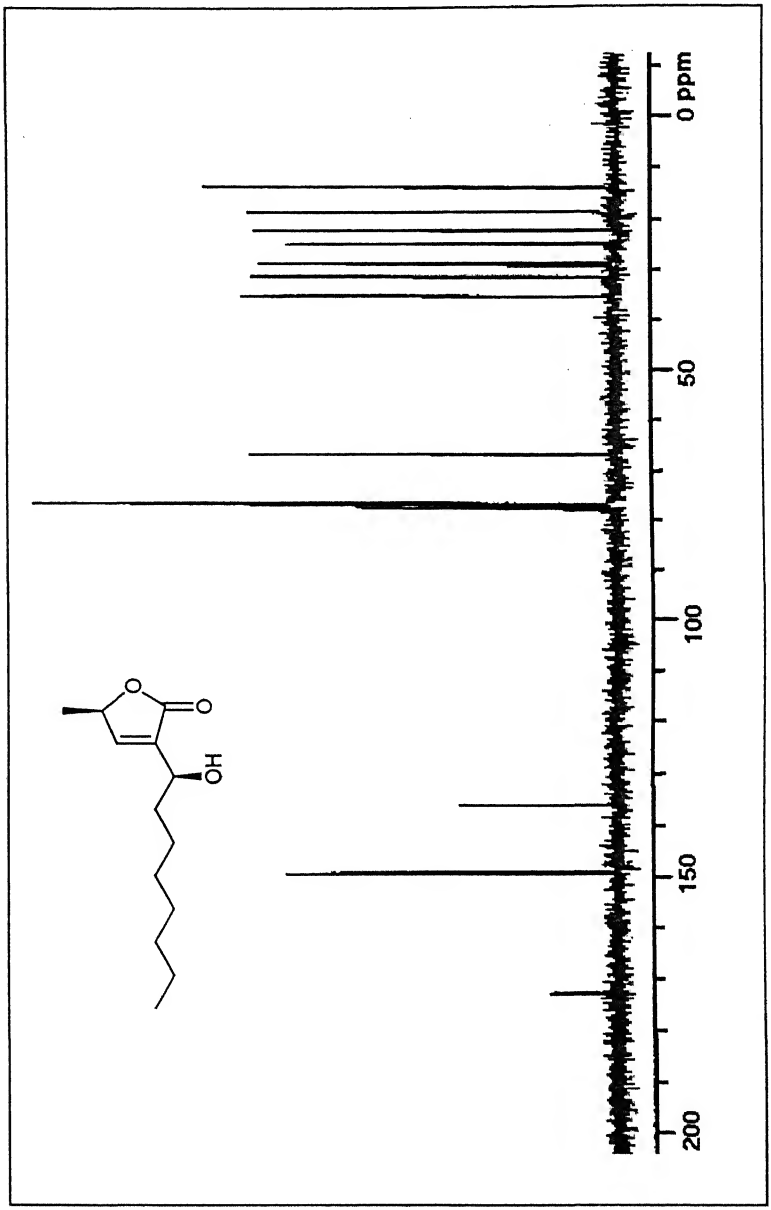


Figure 2.16 ^{13}C NMR of **86**

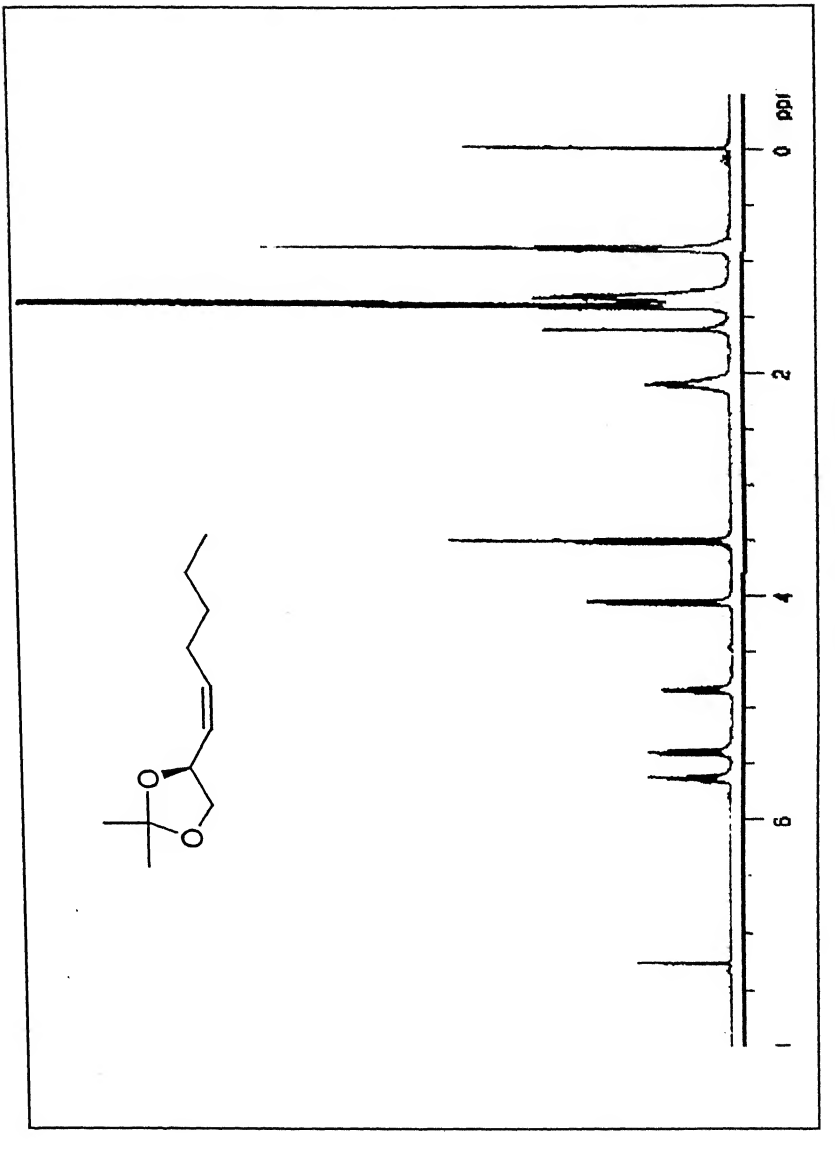


Figure 2.17 ^{1}H NMR of **115**

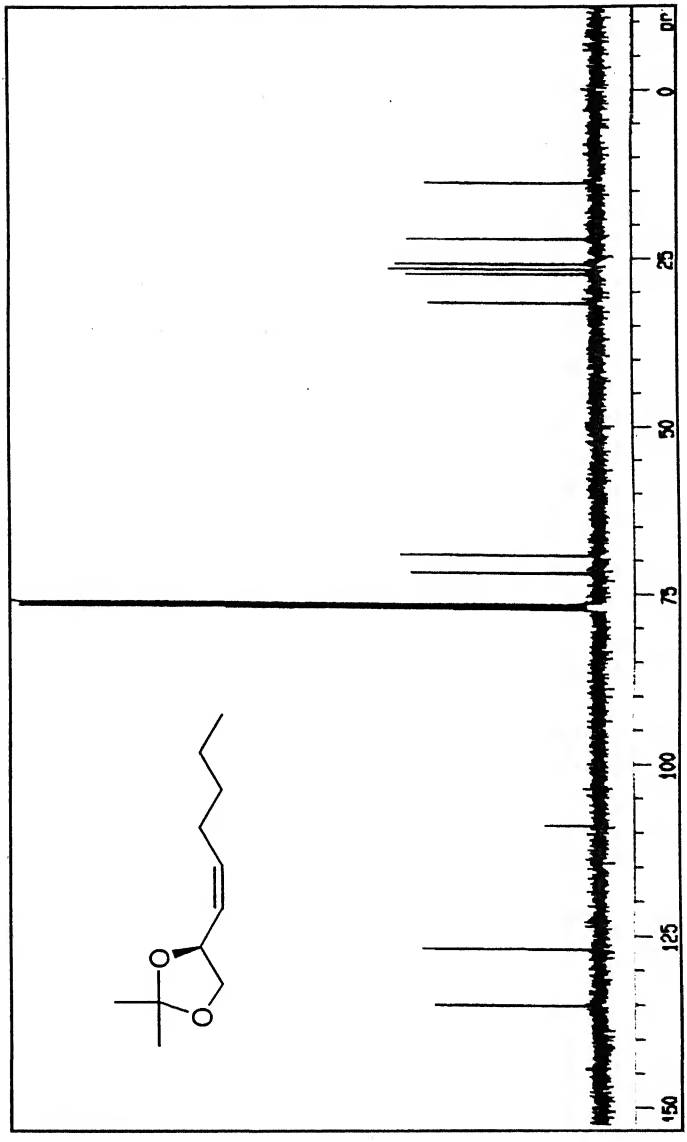


Figure 2.18 ^{13}C NMR of **115**

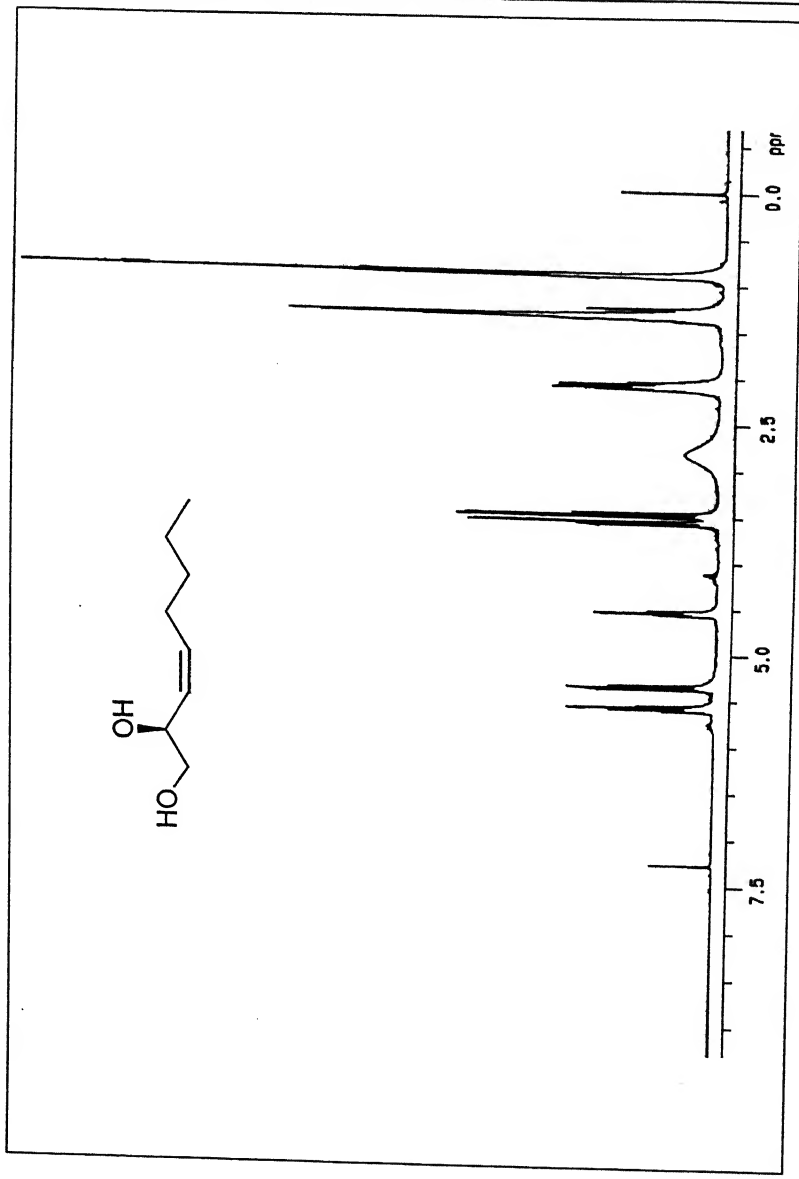


Figure 2.19 ^{1}H NMR of **119**

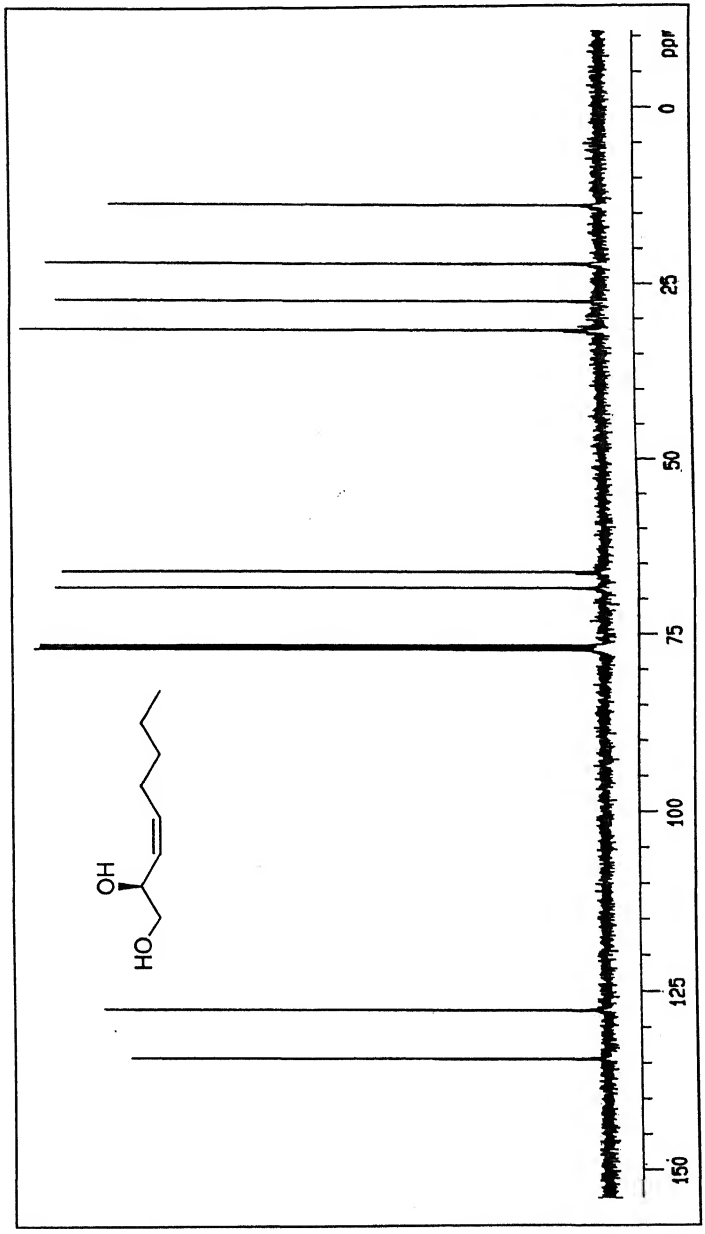


Figure 2.20 ^{13}C NMR of **119**

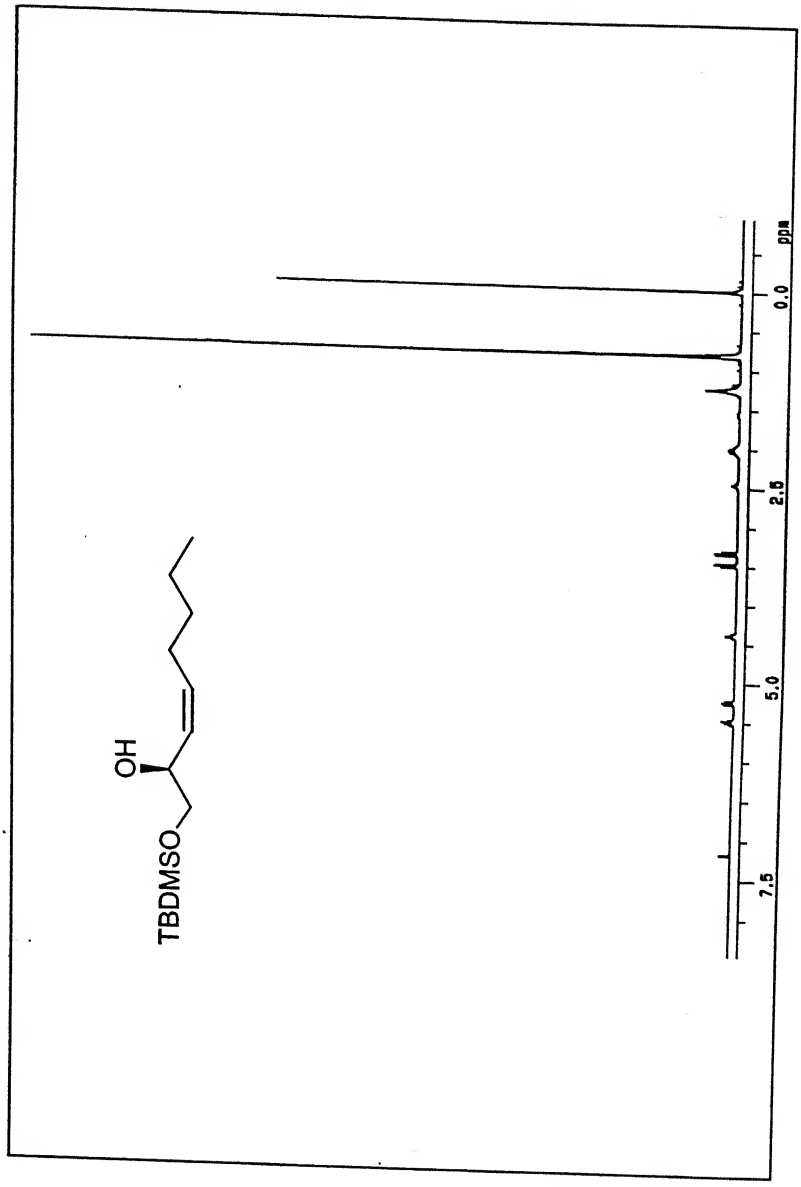


Figure 2.21 ^{1}H NMR of **120**

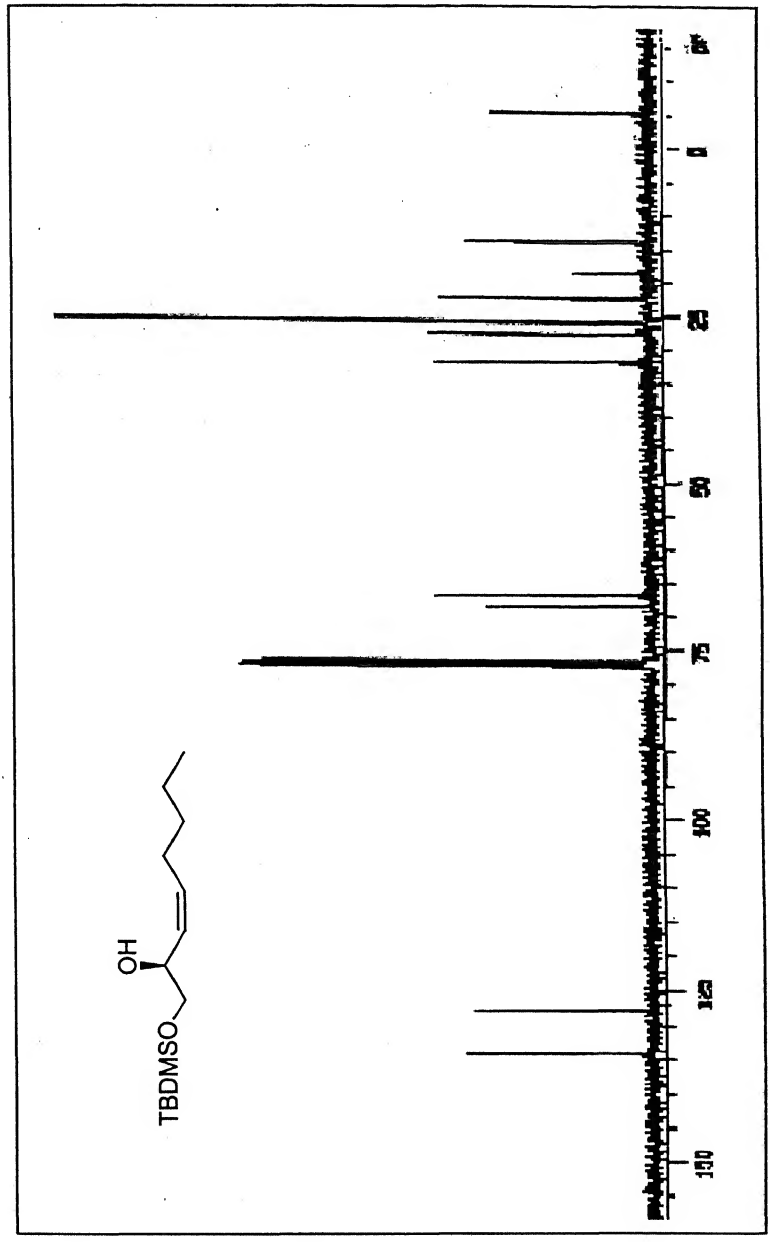


Figure 2.22 ^{13}C NMR of **120**

Chapter 3

A RCM based approach towards synthesis of (+)-diplodialide A and antimycin A_3.

3.1 Introduction:

After the successful synthesis of (-)-acaterin **84** by RCM, we shifted our attention towards macrocyclic lactones. We came across many naturally occurring biologically important macrolides and chose (+)-diplodialide A (**123** A) and Antimycin A_3 **124** as targets. Since RCM based approach is not known in the literature for these two macrolides, we decided to apply this methodology (RCM) for their synthesis.

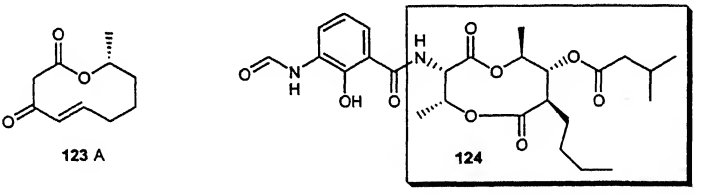


Figure 3.1

The diplodialides (**123** A to D) are the family of ten-membered ring macrocyclic lactones isolated from the pathogenic fungus *Diplodia pinea*.[98] Wada and co-workers have shown that diplodialide A (**123** A) had a significant inhibitory activity against progesterone 11α-hydroxylase in vegetable cell cultures of *Rhizopus stolonifer* at 125 ppm.[99] Subsequently, another ten membered lactone of this family, phoracantholide was isolated from the metasternal gland secretion of *Phoracantha synonyma* by Moore *et al.*[100]

Different methods are available in the literature for the construction of the macrolide core of diplodialide A (**123** A). In this section, we discuss some of the previous known reports for the synthesis of **123** A.

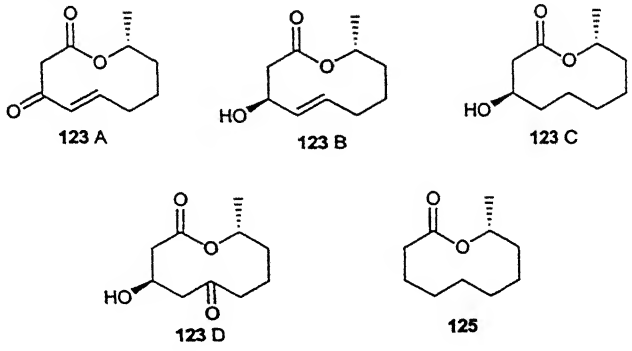
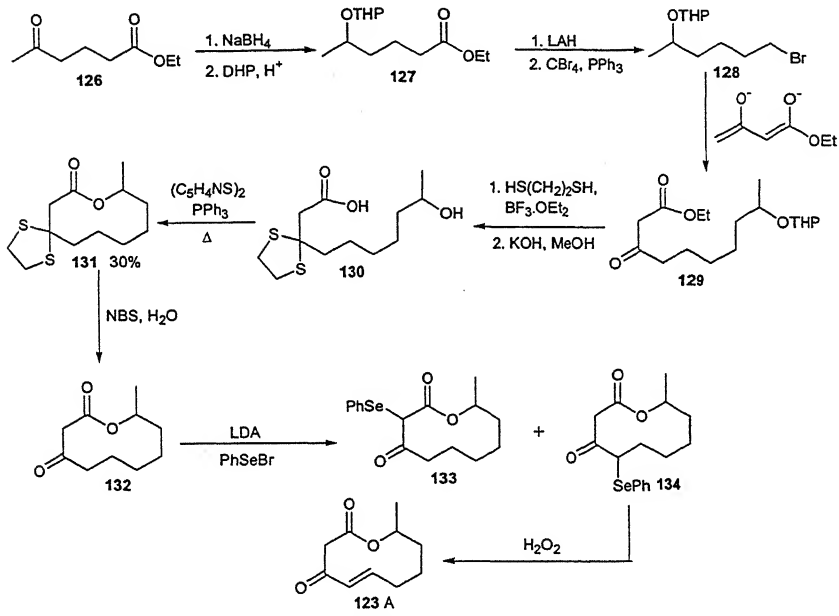


Figure 3.2

The first synthesis of (+/-) diplodialide A (**123** A) was also that of Wada in 1977 (Scheme 3.1).[101] Ethyl-5-oxohexanoate **126** was reduced with $NaBH_4$ and the resulting alcohol protected with DHP to give **127**. Reduction of ester moiety to a primary alcohol followed by conversion to the bromide **128** was achieved by conventional means. Alkylation of the dianion of ethyl acetoacetate with **128** afforded the β-keto ester **129**, which possesses all the carbons required for the construction of diplodialides. Protection of the ketone as the dithiane using BF_3OEt_2 and ethanedithiol, which caused concomitant cleavage of the THP ether, followed by basic hydrolysis of the ethyl ester, furnished acid **130**. Lactonization using Corey procedure afforded macrocycle **131** in 30% yield. Removal of the dithioketal with NBS in water gave the keto lactone **132**. The double bond was then introduced

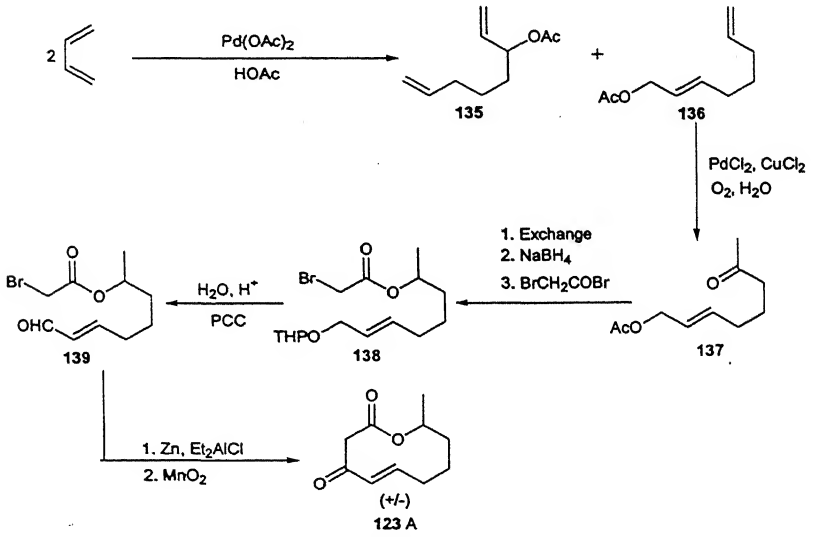
by selenylation-oxidation sequence. Accordingly, treatment of **132** with excess LDA followed by phenylselenyl bromide afforded selenyl lactone **133**, the desired lactone **134** and the recovered starting material **132**. Synthetic diplodialide A (**123** A) was then obtained from **132** after oxidation and selenoxide elimination.



Scheme 3.1

Tsuji published a synthesis of **123** A utilizing an intramolecular Reformatsky reaction for the construction of the 10-membered ring (Scheme 3.2).[102] When butadiene was reacted in the presence of $Pd(OAc)_2$ and acetic acid, diene acetates **135** and **136** were formed. The desired terminal acetate **136** was converted into the ketone **137** by Wacker oxidation. After substitution of THP ether for the acetate, the

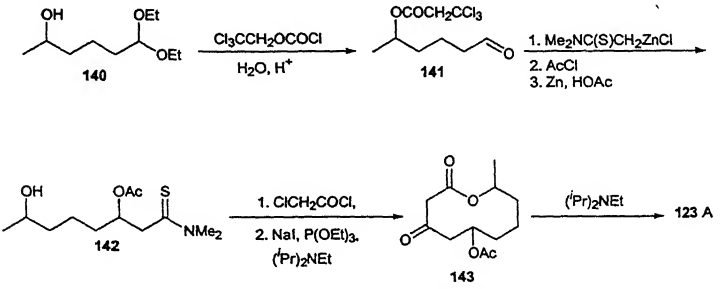
ketone was reduced and the resulting alcohol was acylated with bromoacetyl bromide to afford **138**. Acidic cleavage of the THP ether followed by oxidation provided the ester aldehyde **139**. Final ring closure was achieved using a modified version of Reformatsky reaction. Thus, treatment of **139** with zinc and diethyl aluminium chloride gave a mixture of diastereomeric alcohols in 48% yield. Oxidation of the allylic alcohol with MnO_2 then afforded the synthetic **123** A.



Scheme 3.2

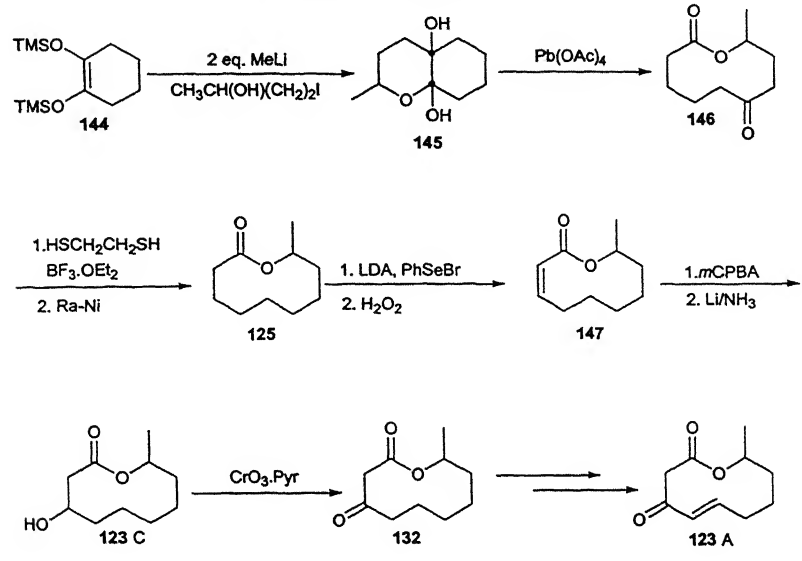
Ireland utilized a sulfide ring contraction process for the ring-forming step of his synthesis of **123** A (Scheme 3.3).[103] The diethyl acetal of 5-hydroxyhexanal **140** was converted to the trichloroethyl carbonate and the acetal hydrolyzed to produce the aldehyde **141** in 86% yield. Addition of the zinc enolate of *N,N*-

dimethylethanethioamide to **141** afforded an intermediate, which was subjected to acylation and reductive carbonyl cleavage to yield **142**. Acylation with chloroacetyl chloride was followed by ring closure to give the macrocycle **143** in 24% yield. Elimination of acetic acid from **143** afforded diplodialide A (**123** A).



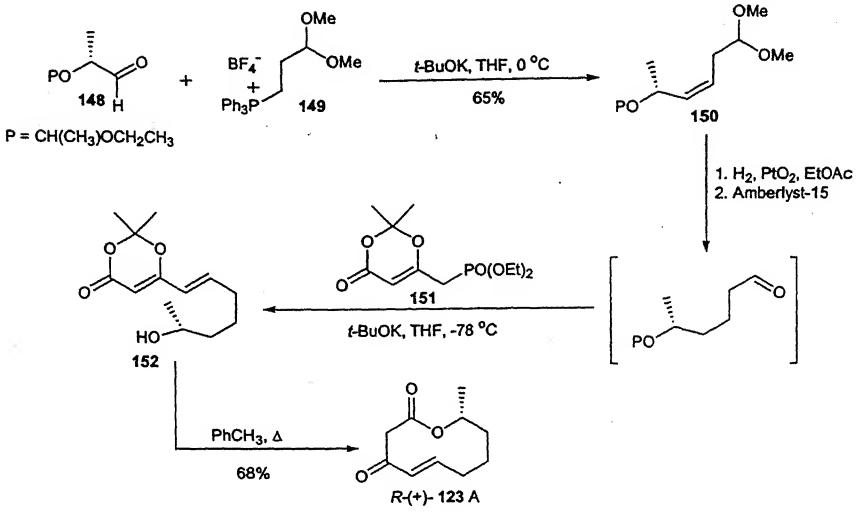
Scheme 3.3

The studies of Wakamatsu culminated in the preparation of three natural compounds from a single synthetic route (Scheme 3.4).[104] The enediol bis silyl ether **144** was converted to the dianion and immediately alkylated with 1-iodo-3-butanol to give glycol **145** as a mixture of diastereomers in 87% yield. Diol fragmentation with lead tetraacetate afforded ketolactone **146** in quantitative yield. Formation of the dithioketal and subsequent Raney Nickel desulfurization gave **125**. Macrocyclic lactone **125** is the simple natural product phoracantholide I. The lactone **125**, on selenation-elimination sequence, furnished the unsaturated lactone **147**. Epoxidation of **147** followed by lithium-ammonia reduction gave diplodialide C (**123** C), which on oxidation gave the β-keto lactone **132**. The β-keto lactone was converted to diplodialide A (**123** A) by literature known sequence.[101]



Scheme 3.4

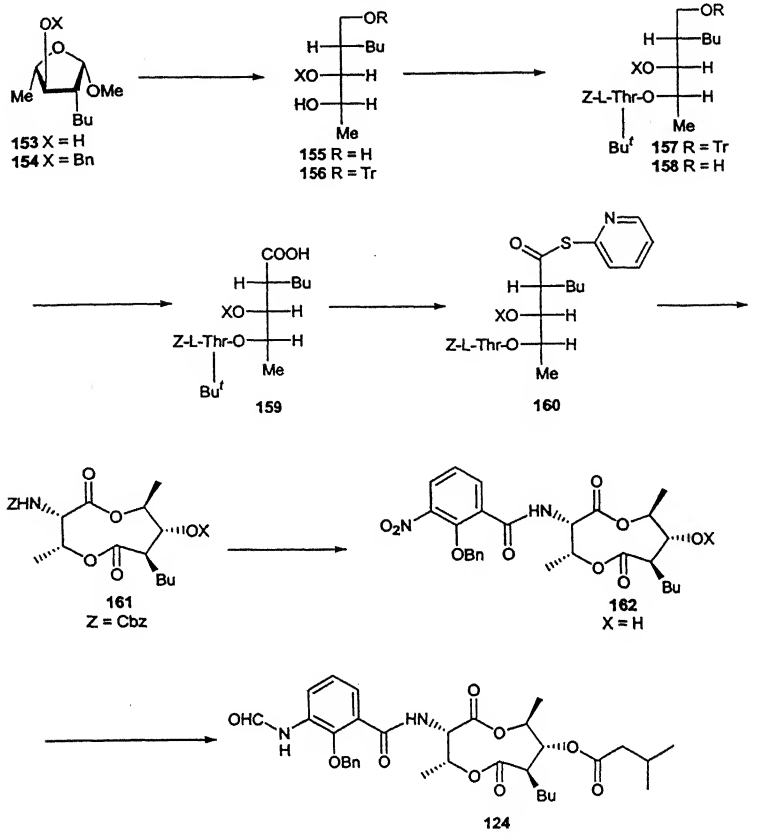
Boeckman and co-workers have described the intramolecular ring opening of dioxolinones by alcohol nucleophile to form the macrocyclic core of diplodialide A (**123** A) (Scheme 3.5).[105] The required optically pure cyclization substrate, dioxolenone alcohol **152**, was obtained in a straightforward way beginning with the protected *R*-(+)-aldehyde **148**. Wittig reaction of **148** with the ylide derived from phosphonium fluoroborate **149** afforded exclusively the *Z* olefin **150**. After catalytic reduction and deprotection, the resulting hydroxy aldehyde was condensed with **151** to afford **152**, which on thermolysis in toluene at reflux gave (+)-diplodialide (**123** A). This is the only report known in the literature for the synthesis of (+)-diplodialide A (**123** A) in enantiomerically pure form.



Scheme 3.5

Antimycin A_3 **124**, a unique unsymmetrical nine-membered dilactone isolated from a number of *Streptomyces* strains,[106] exhibits both antibiotic and antifungal activity.[107] Among the components of antimycin A complex , A_3, which is available from Sigma Co., is one of the most active agents and has been widely used in biological and biochemical investigations.[108] In this section, we discuss few of the literature known reports for the synthesis of Antimycin A_3 **124**.

Kinoshita and co-workers achieved the first total synthesis[109] of Antimycin A_3 starting from methyl 2-*C*-butyl-2,5-dideoxy-β-*L*-arabinofuranoside **153** (Scheme 3.6). The compound **153** was converted to its corresponding benzyl ether **154** which on acid hydrolysis followed by reduction with $NaBH_4$ gave (2*S*,3*R*,4*S*)-3-*O*-benzyl-2-butyl-1,3,4-pentanetriol **155** in 94% yield.

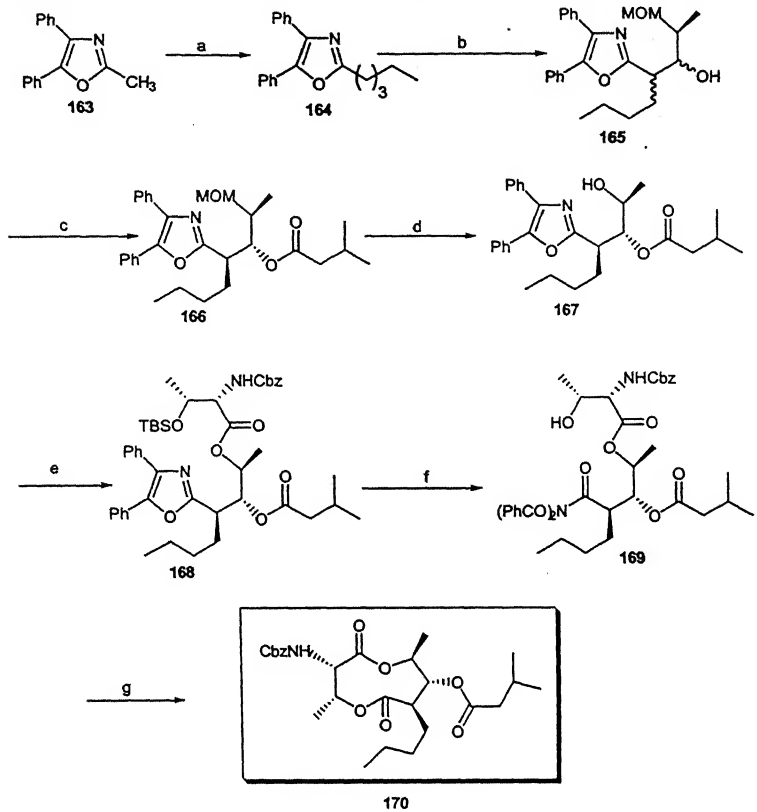


Scheme 3.6

Tritylation of **155** with triphenyl methyl chloride in pyridine at 40 °C gave the 3-*O*-benzyl-1-*O*-trityl-1,3,4-pentanetrioi **156** quantitatively. Acylation of the 4-hydroxyl group of **156** with excess *N*-(benzyloxycarbonyl)-*O*-*t*-butyl-*L*-threonine in the presence of DCC and pyridine afforded the condensation product **157** in 74% yield. Detritylation of **157** with 90% acetic acid gave the corresponding alcohol **158**, which on oxidation with CrO_3.Pyr afforded the ester acid **159**. The *t*-butyl group of **159** was removed by treatment with

trifluoroacetic acid to give an intermediate, which was converted into the corresponding 2-pyridine thiol ester **160** by action of di-2-pyridyl disulfide and triphenylphosphine. The thioester **160**, on macro-lactonization using Corey-Nicolaou procedure,[110] gave the macrocyclic lactone **161** in 14% yield. Hydrogenolysis of **161** with Pd black in methanol under H_2 atm gave a hydroxy amine intermediate, which on *N*-acylation with 2-benzyloxy-3-nitrobenzoicacid *N*-hydroxy-succinimide ester[111] afforded **162**. The *N*-acylamino hydroxy dilactone **162** was *O*-acylated with isovaleric anhydride in pyridine to afford an ester intermediate, which on hydrogenolysis with H_2/Pd followed by *N*-formylation gave the synthetic antimycin A_3 **124**.

Wasserman and co-workers have developed a new method for the construction of macrolide core of antimycin A_3 **124** by photooxygenation of substituted 2-alkyl-4,5-diphenyloxazoles.[112] Thus, 2-methyl-3,4-diphenyloxazole **163** was alkylated with 1-iodobutane in standard fashion yielding **164**, which was treated with *n*-BuLi followed by addition of (*S*)-2-[(methoxy)methoxy]propanal to give **165** as a mixture of diastereomers. The hydroxy derivative **165**, on acylation with isovaleryl chloride in pyridine gave the corresponding ester **166**, which on deprotection with BF_3OEt_2 and thiophenol afforded the hydroxy oxazole **167**. The isomer **167** was then condensed with *N*-carbobenzyloxy-*O*-*t*-butylsilyl-*L*-threonine in the presence of DCC and DMAP to provide the ester **168**.



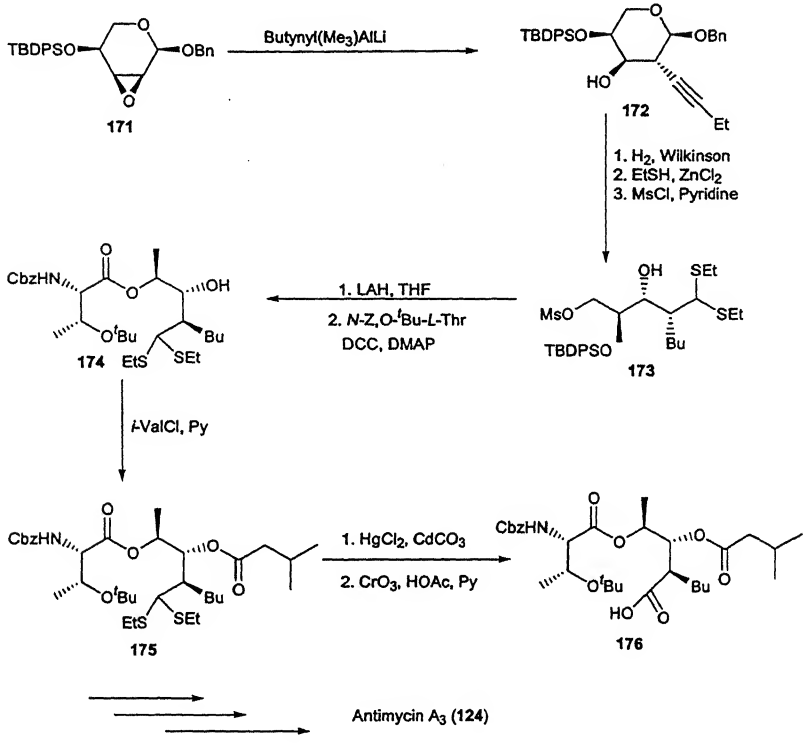
Conditions: (a) *n*-BuLi, *n*-BuI, -78 °C, THF; (b) *n*-BuLi, (*S*)-2-[(methoxy) methoxy] propanal, THF, -78 °C; (c) $ClCOCH_2CH(CH_3)_2$, pyridine; (d) $BF_3.OEt_2$, PhSH, CH_2Cl_2; (e) DCC, DMAP, CH_2Cl_2, *N*-carbobenzyloxy-*O*-*t*-butylsilyl-*L*-threonine; (f)(i) *n*-Bu_4NF, THF, 0 °C; (ii) $^1O_2$, CH_2Cl_2, Sensitox, 25 °C, 3h; (g) PPTS, xylenes, heat.

Scheme 3.7

The TBDMS ether of **168** was removed under TBAF condition to give ω-hydroxy oxazole intermediate, which on dye-sensitized photooxygenation led cleanly to the activated triamide **169**. The triamide **169** was cyclized to the dilactone **170** in 20% yield by refluxing **169** with PPTS in Xylenes. Since the synthesis of antimycin

A_3 from the dilactone **170** is known in the literature,[109] they stopped their synthesis at this stage (Scheme 3.7).

The schematical representation of Frejd's approach to antimycin A_3 is presented in Scheme 3.8.



Scheme 3.8

The starting point of their synthesis was 2,3-anhydro-α-*L*-riboside **171**, prepared from *L*(+)-arabinose. Reaction of **171** with lithium butynyl(trimethyl)aluminate afforded the 2-deoxy-2-*C*-butynyl sugar **172** in 68% yield. Chemoselective reduction of the triple bond of **172** by Wilkinson catalyst followed by ring cleavage by EtSH in the

presence of $ZnCl_2$ gave the acyclic diol intermediate, which on selective primary mesylation provided the dithio mesylate **173**. Reduction of **173** with $LiAlH_4$ followed by condensation with *N*-carbobenzyloxy-*O*-*t*-butyl-*L*-threonine in the presence of DCC and DMAP gave the dithio ester **174**. The hydroxy group of **174** was acylated with isovaleryl chloride and pyridine to provide **175**, which on treatment with $HgCl_2$ in the presence of $CdCO_3$ followed by oxidation with CrO_3.pyr gave the acid **176**. The acid was converted into antimycin A_3 **124** by a known procedure.[109]

There are few more syntheses[114] available for antimycin A_3 **124** that are not mentioned here, as they are not relevant to our work.

In this chapter, we wish to report our efforts directed toward the synthesis of (+)-diplodialide A (**123** A) and the macrocyclic core of Antimycin A_3 **124** using ring-closing metathesis.

3.2. Background:

The construction of the macrocyclic ring core of any macrocyclic lactone natural product is a challenging task in synthetic organic chemistry.[115] Over the past two decades, there has been intense interest in the development of methodology for the formation of macrocyclic ring lactones, since this framework is one of the basic structures for natural and unnatural useful organic molecules.[116] Although there are several methods available for macrolactonization,[117] the yield in the lactonization of ω-hydroxy acids by using most of these reported reagents is not always good, even under high dilution conditions and the corresponding dilactones are preferentially formed in many cases. Very recently, olefin metathesis has been proved to be the highly flexible method for the construction of macrocyclic rings.[8] Hundreds of naturally occurring macrocyclic lactones have been synthesized using ring closing metathesis (RCM) as a key step.[8]

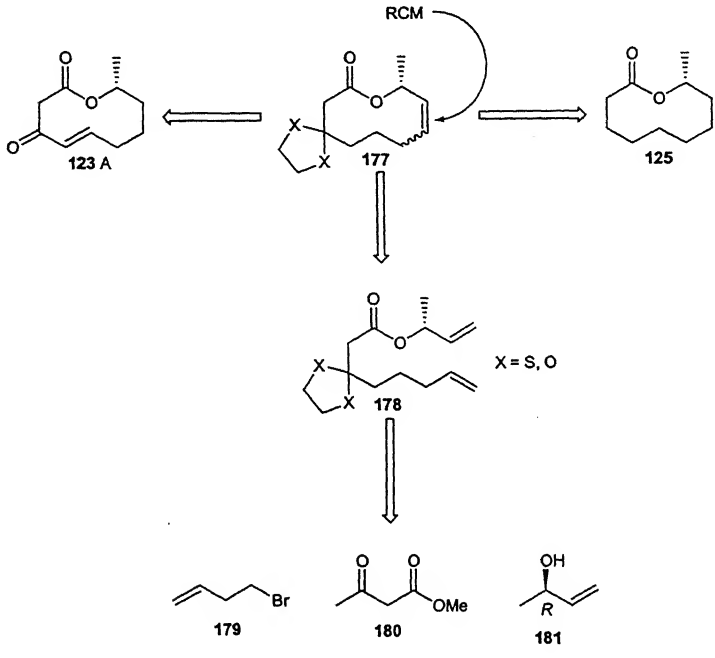
Diplodialides (**123** A-D) (Figure 3.2) are the family of ten-membered macrocyclic lactones isolated from the pathogenic fungus *Diplodia pinea* by Wada and co-workers.[99] Among the four (**123** A-D), diplodialide A (**123** A) showed a significant inhibitory activity against progesterone 11α-hydroxylase in vegetable cell cultures of *Rhizopus stolonifer* at 125 ppm.[99] Extensive studies have been reported in the literature for the construction of 10-membered lactone unit of (+/-)-diplodialide A (**123** A),[7] which include macrolactonization using Corey's procedure,[101] sulfide ring contraction,[103] intramolecular Reformatsky reaction[102] etc. It should be noted that in all the cases, the

yield of products in cyclization step was less than 30%. Boeckman reported the first asymmetric synthesis of (+)-diplodialide A (**1** A) *via* intramolecular ring opening of dioxolenones by alcohol nucleophiles.[105] Although, in this particular case, the yield of product in cyclization step was moderate (68%), it required very harsh conditions. These observations clearly show that there is a need for a flexible method towards the construction of the 10-membered lactone unit of (+)-diplodialide A (**1** A). Since, RCM has been emerged as a powerful tool for the construction of macrocyclic molecules, we started working towards synthesis of (+)-diplodialide A (**123** A) by using this methodology.

During our progress towards synthesis of (+)-diplodialide A (**123** A), we came across another interesting naturally occurring 9-membered dilactone called Antimycin A_3 **124**, isolated from a number of *Streptomyces* strains.[106] In this chapter, we also discuss our efforts directed towards synthesis of Antimycin A_3 **124** using RCM approach.

3.3. Present Work:

A careful retrosynthetic analysis showed that both (+)-diplodialide (**123** A) and (*R*)-phoracantholide[118] **125** could be obtained from a common intermediate **177** through simple steps (Scheme 3.9).

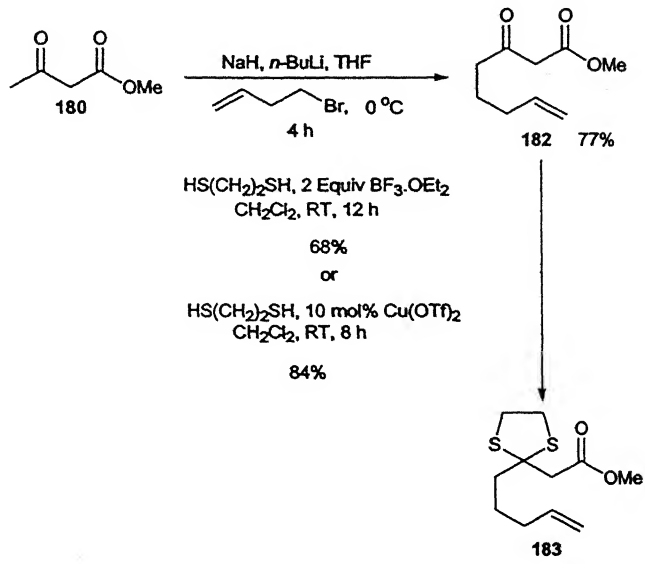


Scheme 3.9

The lactone **177** can be obtained from the diene ester **178** *via* ring closing metathesis. The metathesis precursor **178** can be constructed starting from methyl acetoacetate **180**, homoallyl bromide **179** and (*R*)-3-buten-2-ol **181** through simple transformations.

Thus, our approach towards synthesis of (+)-diplodialide (**123** A) starts from a commercially available and inexpensive methyl acetoacetate **180**. The dianion of methyl acetoacetate **180** was treated

with 4-bromo-1-butene in THF at 0 °C for 4 h afforded the β-keto ester **182** in 77% yield (Scheme 3.10).

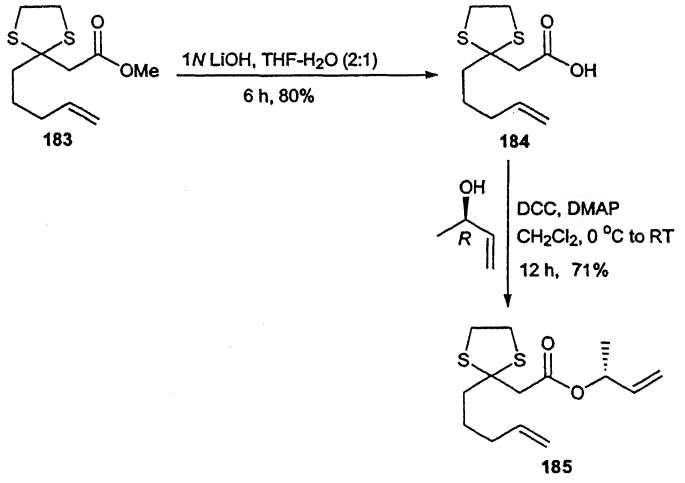


Scheme 3.10

Next, we wanted to protect the carbonyl group and then hydrolyze the ester. We chose thio-ketal as the protecting group, because by using this protecting group it is possible to get both (+)-diplodialide (**123** A) and (*R*)-phoracantholide **125** from **177** by deprotection and reduction respectively (Scheme 3.9). Thus, treatment of **182** with ethanedithiol in the presence of 2 equivalent of BF_3OEt_2[119] gave the desired thioketal **183** in only 68% yield after 12 h. Since, thioacetalization of carbonyl compounds is being a Lewis acid catalyzed transformation, we carried out the same reaction in the presence of catalytic amount of $Cu(OTf)_2$. It was heartening to see that thioacetalization proceeded very smoothly and the product **184** was

obtained in 84% yield after 8 h (Scheme 3.10). We have done systematic literature survey and found that there was no report for thioacetalization using $Cu(OTf)_2$ as a catalyst. So, we explored this methodology by using a variety of aldehydes and ketones and the results will be discussed in Part B.

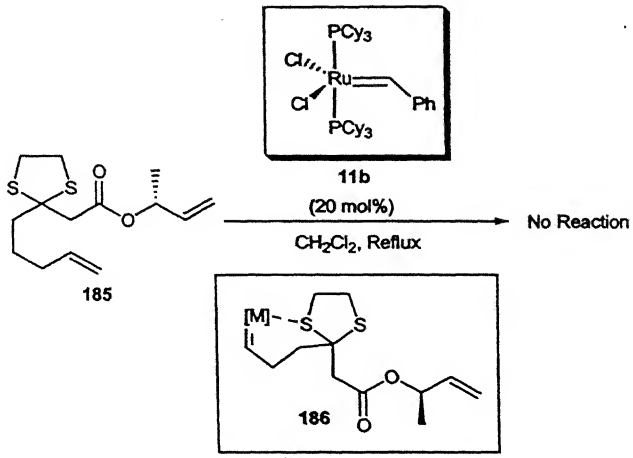
Ester hydrolysis of **183** was carried out by using 1*N* aq. LiOH solution in THF:H_2O (2:1) mixture to give the acid **184** in 80% yield. The acid **184** was then condensed with (*R*)-3-buten-2-ol **181** in the presence of DCC and DMAP to afford the diene ester **185**, a substrate for metathesis reaction, in 71% yield (Scheme 3.11).



Scheme 3.11

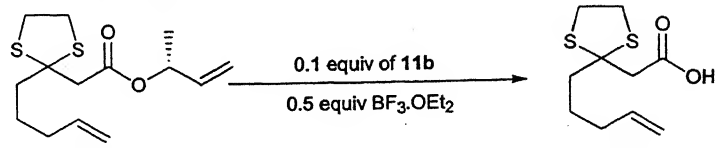
Ring closure reaction of **185** was carried out by using 20 mol% of Grubbs catalyst **11b** in refluxing CH_2Cl_2. Unfortunately, in this case, no cyclized product was observed. The reason is probably due to the

deactivation of Ru catalyst[120] by coordination of sulfur atom to form a stable chelate **186** (Scheme 3.12).



Scheme 3.12

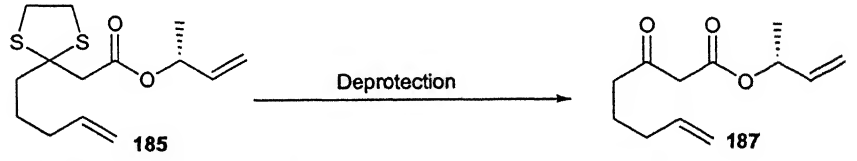
The use of second-generation catalysts, like **26**, also didn't help in this regard. In fact, an inseparable complex mixture of products was obtained when we tried to cyclize the diene **185** in the presence of 10 mol% of **26** in refluxing CH_2Cl_2. Then, we planned to decrease the coordination ability of the sulfur atoms by adding a catalytic amount of BF_3OEt_2. The logic behind this was that BF_3OEt_2 would coordinate to the sulfur atoms prior to Ru catalyst and thereby reducing the coordination ability of sulfur towards Ru center. But surprisingly, exposure of **185** to 10 mol% of Grubbs catalyst **11b** in the presence of 50 mol% of BF_3OEt_2 gave the hydrolyzed product **184** in 15% yield along with unreacted starting material (Scheme 3.13). Although, BF_3OEt_2 is known to cleave methyl esters,[121] in our case allyl ester group got hydrolyzed.



185 184

Scheme 3.13

Since, the thioacetal group gave problem in ring closure step, we have decided to deprotect it and then carry out the metathesis reaction. .We carried out the dethioacetalization of **185**, by using various methods (Scheme 3.14). Among various methods tried, (diacetoxy)iodobenzene was found to be the better reagent for this transformation. Thus, treatment of **185** with 1.5 equivalent of (diacetoxy)iodobenzene in MeOH-Water mixture gave the desired β-ketoester **187** in 35% yield.



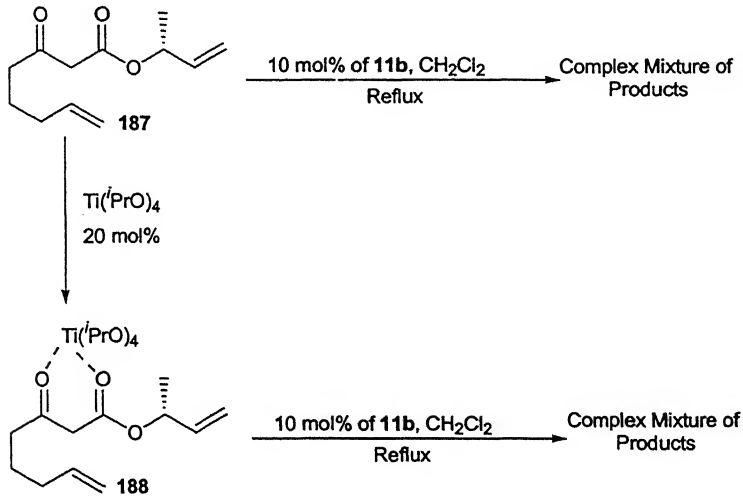
185 187

Conditions: 1. CAN, 75% aq. CH_3CN, RT, 30 min. Decomposition[122a]
2. Chloramine-T, 25% aq. MeOH, RT. No Reaction[122b]
3. H_5IO_6, MeOH:H_2O, RT. <25% Product[122c]
4. $Bi(NO_3)_3.5H_2O$, C_6H_6, RT. No Reaction[122d]
5. NBS, H_2O, RT. <30% Product[122e]
6. Clayan, CH_2Cl_2, RT. No Reaction[122f]
7. $Hg(OAc)_2$, CH_2Cl_2, RT. Decomposition[122g]
8. $PhI(OAc)_2$, MeOH:H_2O, RT. 35% Product[122h]

Scheme 3.14

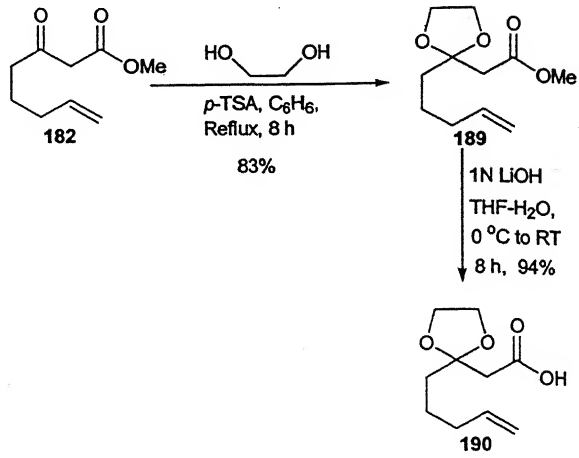
The cyclization of **187** in the presence of 10 mol% of **11b** in refluxing CH_2Cl_2 again gave a complex mixture of products, which

were not separable in column chromatography. The addition of $Ti(^iPrO)_4$[123] also didn't help to get clean reaction products (Scheme 3.15).



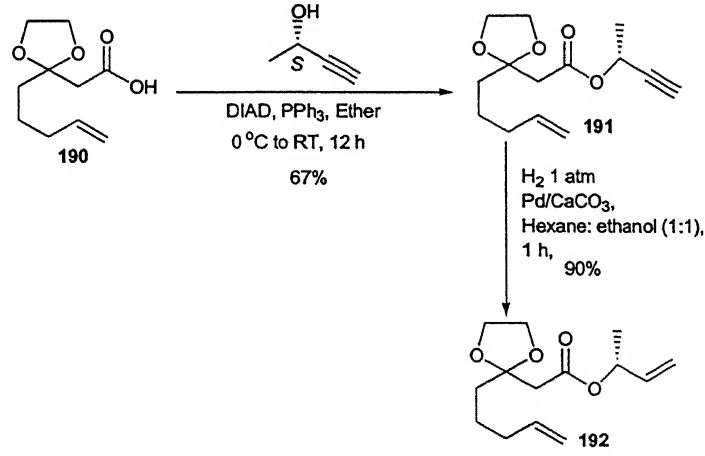
Scheme 3.15

Since, the unprotected ketone in **187** also gave problem in cyclization step, we decided to change the protective group. This time, we chose simple acetal as the protecting group. Thus, treatment of **182** with ethylene glycol in the presence of a catalytic amount of *p*-TSA gave the desired ketal **189** in 83% yield. The methyl ester group of **189** was hydrolyzed using 1*N* aq. LiOH solution to provide the acid **190** in 94% yield (Scheme 3.16).



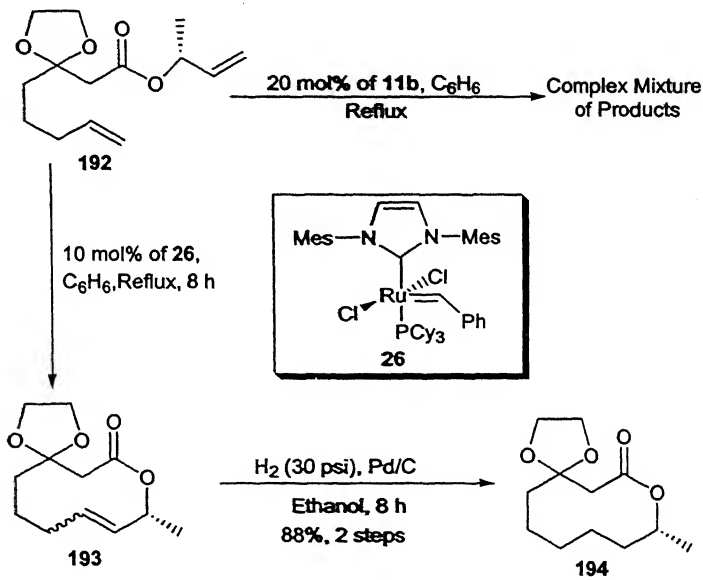
Scheme 3.16

The acid **190** on Mitsunobu reaction with (*S*)-3-butyn-2-ol in the presence of DIAD and PPh_3 provided the alkyne ester **191**, which on Lindlar reduction with $Pd/CaCO_3$ in the presence of catalytic amount of quinoline under H_2 atm gave the metathesis precursor **192** in 90% yield (Scheme 3.17).



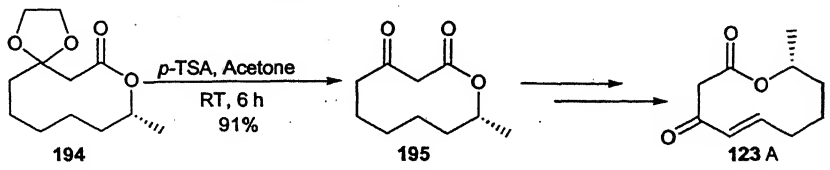
Scheme 3.17

We then carried out cyclization of the diene ester **192** in the presence of 20 mol% of Grubbs catalyst **11b** in refluxing benzene under high dilution conditions, but unfortunately we again got a complex mixture of products. But the same reaction when we carried out in the presence of 10 mol% of the second generation Grubbs catalyst **26**, we got the desired cyclized product **193** as a mixture of *cis* and *trans* isomers which was directly reduced with Pd/C under H_2 atmosphere (30 psi) to provide the saturated lactone **194** in 88% yield (Scheme 3.18).



Scheme 3.18

Deprotection of the ketal moiety in **194** using catalytic amount of *p*-TSA in wet acetone gave the β-keto lactone **195** in 91% yield (Scheme 3.19). Since, the conversion of **195** to (+)-diplodialide A (**123** A) is known in the literature,[101] we stopped our synthesis at this stage.

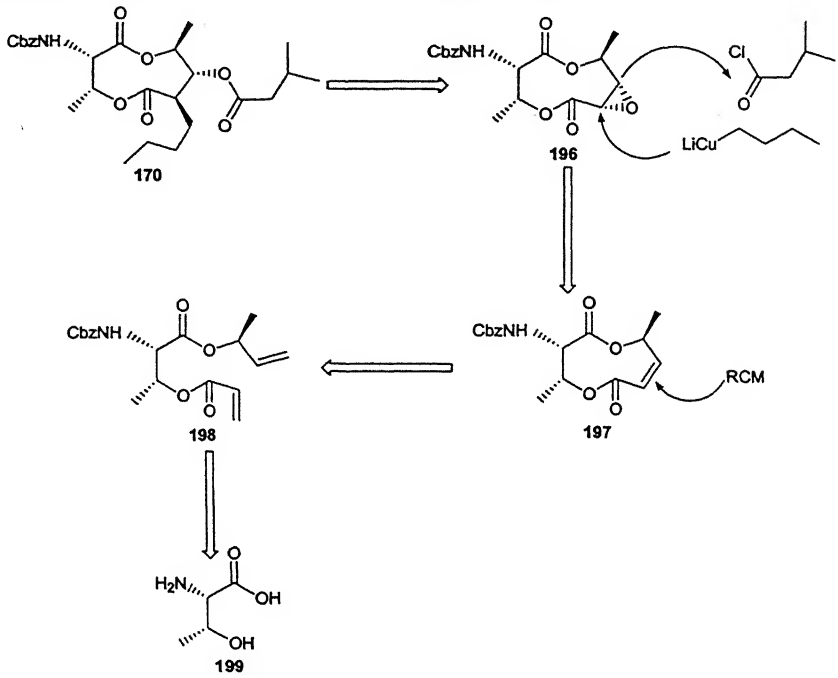


Scheme 3.19

Finally, we have achieved a formal synthesis of (+)-diplodialide A (**123** A) using ring closing metathesis as a key step. The overall yield of the β-ketolactone **195** by our method is 29%, which is very high in comparison with other literature known methods.[101,103]

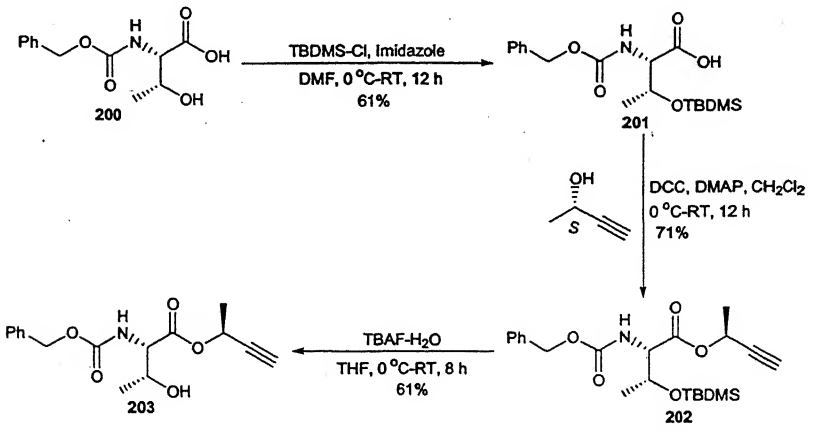
During our progress towards synthesis of (+)-diplodialide A (**123** A), we came across another interesting molecule Antimycin A_3 **124**, which is a 9-membered dilactone natural product isolated from a number of *Streptomyces* strains.[106] Since, there is no report in the literature for the synthesis of this molecule using RCM, we started working towards synthesis of the macrocyclic core of antimycin A_3 by applying this methodology.

Since, the conversion of the macrocycle **170** to antimycin A_3 is known in the literature, we have chosen **170** as our target. A careful retrosynthetic analysis of **170** showed that it could be obtained from the dilactone epoxide **196** through epoxide ring opening with butyl cuprate followed by addition of isovaleryl chloride (Scheme 3.20). The dilactone epoxide **196** can be formed by epoxidation of *cis*-α,β-unsaturated dilactone **197**, which in turn, can be obtained from an acyclic diene **198** *via* ring closing metathesis. The acyclic diene could be prepared from *L*-threonine **199**, a commercially available amino acid, through simple steps.



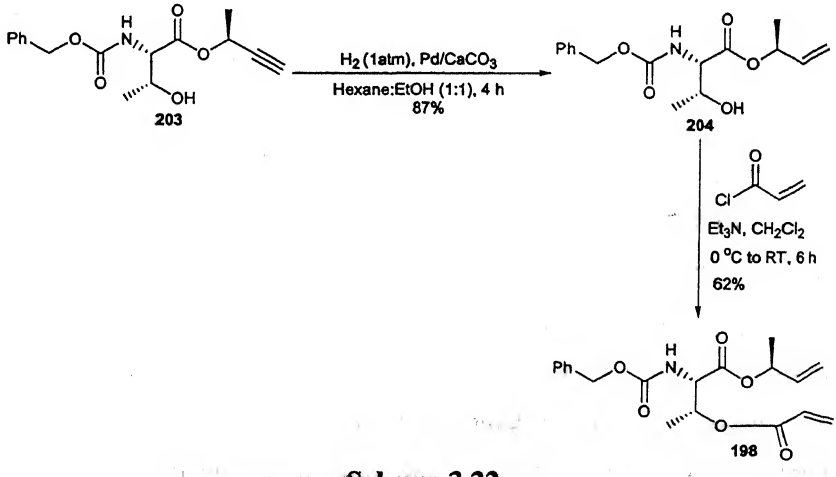
Scheme 3.20

First, the starting material *L*-threonine **199** was converted into its corresponding Cbz-derivative **200** by literature known procedure.[124] Treatment of **200** with TBDMS-Cl in the presence of imidazole gave the silyl ether protected acid **201** in 61% yield (Scheme 3.21).[112b] Esterification of **201** with (*S*)-3-butyn-2-ol in the presence of DCC and DMAP afforded the desired alkyne ester **202** in 71% yield. The silyl ether group of alkyne ester was deprotected with TBAF-H_2O in THF to provide the hydroxy alkyne ester **203** in 61% yield (scheme 3.21).



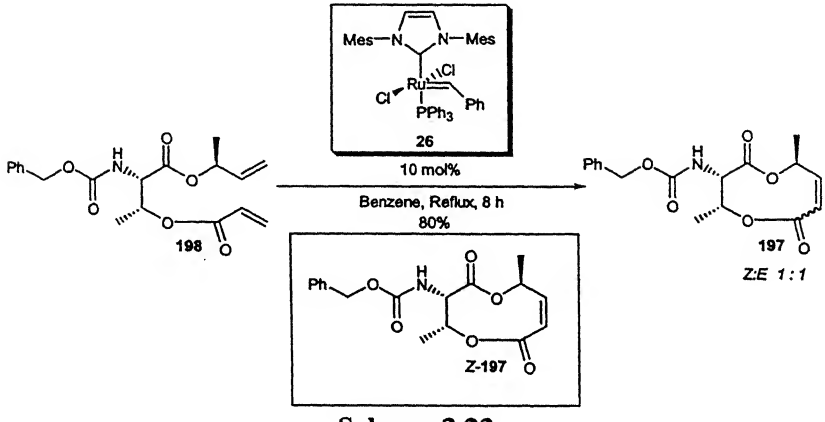
Scheme 3.21

Selective Lindlar reduction of the alkyne moiety in **203** was achieved with a catalytic amount of $Pd/CaCO_3$ in H_2 atmosphere (1 atm) to give 87% yield of the hydroxy alkene **204**, which was acroylated with acryloyl chloride and triethyl amine to afford the diene ester **198**, a metathesis precursor, in 62% yield (Scheme 3.22).



Scheme 3.22

The ring closing metathesis reaction of **198** was carried out by exposing **198** to the second generation Grubbs catalyst **26** (10 mol%) in refluxing benzene under high dilution conditions. It was found that the cyclized product **197** was obtained in 80% yield as a 1:1 mixture of *cis* and *trans* isomers (Scheme 3.23).



Scheme 3.23

We temporarily stopped our synthesis at this stage. Since, only the *Z*-isomer (*Z*-**197**) can be converted to the natural Antimycin A_3, further investigation to improve the *E/Z* ratio of products is currently under progress in our laboratory.

In conclusion, we have accomplished a formal synthesis of (+)-diplodialide A (**123** A) from readily available starting materials. The macrocyclic lactone core of (+)-diplodialide A (**123** A) was constructed in high yield using ring closing metathesis (RCM) strategy. We have also made a RCM based approach to the synthesis of the macrocyclic core of antimycin A_3 (**124**). In the case of antimycinn A_3 synthesis,

further investigation to improve the *Z/E* ratio of the cyclized product is currently under progress.

3.4. Experimental Section:

The common materials and methods have already been given in the experimental section of the chapter 2, Part A. HMPA was distilled over CaH_2 and stored over 4 Å molecular sieves. Benzene and ether were distilled from sodium benzophenone ketyl under nitrogen. *n*-BuLi was obtained from CHEMETALL GmbH Ltd. 1,2-ethanedithiol, $Cu(OTf)_2$, DIAD, benzylidine [1,3-bis(2,4,6-trimethylphenyl)-2-imidazolinylidene] dichloro-(tricyclohexyl phosphine) ruthenium, $BF_3{\cdot}OEt_2$, and acryloyl chloride were obtained from Fluka and used as received. (*S*)-3-bytyne-2-ol was obtained from Lancaster. Lindlar catalyst was obtained from Aldrich Chem. Company.

3-Oxo-oct-7-enoic acid methyl ester 182: Methyl acetoacetate **180** (4.8 mL, 44.4 mmol) was added drop-wise to a stirred suspension of NaH (60 % suspension in mineral oil) (2.13 g, 53.3 mmol) in a mixture of *anhydrous* THF (90 mL) and HMPA (10 mL) at 0 °C. After being stirred for 10 minutes, *n*-BuLi (15% w/v solution in hexane, 21 mL, 48.9 mmol) was added drop-wise to it at 0 °C and the resulting yellow solution was stirred for further 10 min. A solution of 4-bromo-1-butene **179** (2.3 mL, 22.2 mmol) in *anhydrous* THF was then added drop-wise to it and the resulting heterogeneous mixture was stirred at 0 °C for further 4 h. It was warmed to rt and quenched with saturated *aqueous* NH_4Cl solution. The organic layer was separated and the aqueous layer was extracted with ether. The combined organic layer was washed with saturated brine solution and dried over *anhydrous* Na_2SO_4. Evaporation of the solvent under *vacuo* gave the crude product, which on

purification over silica gel column using 2% EtOAc in petroleum ether gave the pure compound **182** as colorless oil. Yield 2.9 g (77 %); R_f 0.65 (20% EtOAc in petroleum ether); FT IR (neat) 1750, 1644 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.70 (quintet, J = 7.6 Hz, 2H), 2.07 (q, J = 7.3 Hz, 2H), 2.55 (t, J = 7.3 Hz, 2H), 3.45 (s, 2H), 3.74 (s, 3H), 4.97-5.06 (m, 2H), 5.71-5.82 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.35, 32.76, 42.08, 49.04, 52.30, 115.40, 137.67, 167.61, 202.53; MS (ES): 171 (M^++1); Anal. Calcd. for $C_9H_{14}O_3$: C, 63.53; H, 8.23. Found: C, 63.42; H, 8.08.

(2-Pent-4-enyl-[1,3]dithiolan-2-yl)-acetic acid methyl ester 183: $Cu(OTf)_2$ (106 mg, 0.29 mmol) was added to a solution of ketoester **182** (500 mg, 2.9 mmol) and 1,2-ethanedithiol (296 µL, 3.5 mmol) in *anhydrous* CH_2Cl_2 at rt and stirred at ambient temperature for further 8 h. The reaction mixture was then diluted with CH_2Cl_2 and washed with 15% NaOH solution followed by saturated brine solution and dried over *anhydrous* Na_2SO_4. Evaporation of solvent gave crude compound, which on purification over silica gel column using 5% EtOAc in petroleum ether provided the pure thioketal **183** as colorless oil. Yield 608 mg (84%); R_f 0.50 (10% EtOAc in petroleum ether); FT IR (neat) 1739 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.60-1.63 (m, 2H), 2.06-2.14 (m, 4H), 3.05 (s, 2H), 3.30 (s, 4H), 3.70 (s, 3H), 4.95-5.05 (m, 2H), 5.75-5.85 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.35, 33.58, 39.65, 42.02, 47.99, 51.68, 66.96, 114.84, 138.32, 170.52; MS (ES): 247 (M^++1); Anal. Calcd. for $C_{11}H_{18}O_2S_2$: C, 53.65; H, 7.32. Found: C, 53.60; H, 7.29.

(2-Pent-4-enyl-[1,3]dithiolan-2-yl)-acetic acid 184: A solution of 1*N* *aqueous* LiOH (20 mL, 20.0 mmol) was added drop-wise to a solution of methyl ester **183** (500 mg, 2.0 mmol) in THF (40 mL) and water (20 ml) mixture at 0 °C. The reaction mixture was then slowly warmed to rt and stirred for additional 6 h. It was again cooled to 0 °C, neutralized with 2*N* HCl and extracted with EtOAc. The combined organic layer was washed with saturated brine solution and dried over *anhydrous* Na_2SO_4. Evaporation of the solvent under *vacuo* followed by purification over silica gel column using 30% EtOAc in petroleum ether gave the pure acid **184** as a pale yellow solid. Yield 370 mg (80%); mp 79-81 °C; R_f 0.50 (50% EtOAc in petroleum ether); FT IR (KBr) 3066-2741 (br), 1709 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.52-1.59 (m, 2H), 1.99-2.08 (m, 4H), 3.04 (s, 2H), 3.25 (s, 4H), 4.90 (td, J = 10.2, 1.2 Hz, 1H), 4.96 (qd, J = 17.1, 1.5 Hz, 1H), 5.69-5.77 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.31, 33.51, 39.68, 41.96, 47.96, 66.55, 114.89, 138.19,175.62; MS (ES): 233 (M^++1); Anal. Calcd. for $C_{10}H_{16}O_2S_2$: C, 51.72; H, 6.90. Found: C, 51.74; H, 6.84.

(2-Pent-4-enyl-[1,3]dithiolan-2-yl)-acetic acid (1*R*)-methyl-allyl ester 185: A solution of DCC (290 mg, 1.4 mmol) in *anhydrous* CH_2Cl_2 (1 mL) was added drop-wise to a stirred solution of the acid **184** (295 mg, 1.27 mmol), (*R*)-3-buten-2-ol **7** (132 µL, 1.53 mmol) and 4-DMAP (117 mg, 0.95 mmol) in *anhydrous* CH_2Cl_2 (4 mL) at 0 °C. After being stirred for additional 12 h at rt, the reaction mixture was filtered through a pad of celite and the filtrate was washed with water, saturated brine solution and dried over *anhydrous* Na_2SO_4. Solvent was

evaporated under reduced pressure to get crude material, which on purification over silica gel column using 2% EtOAc in petroleum ether to give pure ester **185** as colorless oil. Yield 258 mg (71 %); R_f 0.60 (10% EtOAc in petroleum ether); $[\alpha]^{25}_D$ +6.50 (*c* 1.75, $CHCl_3$); FT IR (neat) 1733 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.33 (d, J = 6.4 Hz, 3H), 1.59-1.64 (m, 2H), 2.05-2.14 (m, 4H), 3.05 (s, 2H), 3.29 (s, 4H), 4.96 (td, J = 10.2, 1.0 Hz, 1H), 5.02 (qd, J = 17.0, 1.7 Hz, 1H), 5.15 (td, J = 10.8, 1.2 Hz, 1H), 5.27 (td, J = 17.1, 1.2 Hz, 1H), 5.35-5.41 (m, 1H), 5.75-5.89 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.89, 26.33, 33.57, 39.55, 42.18, 48.32, 67.03, 71.41, 100.54, 114.81, 116.09, 137.40, 138.30, 169.20; MS (ES): 287 (M^++1); Anal. Calcd. for $C_{14}H_{22}O_2S_2$: C, 58.74; H, 7.69. Found: C, 58.70; H, 7.68.

(2-Pent-4-enyl-[1,3]dioxolan-2-yl)-acetic acid methyl ester 189: A solution of ketoester **182** (400 mg, 2.4 mmol), ethylene glycol (395 µL, 7.1 mmol) and *p*-TSA (45 mg, 0.24 mmol) in *anhydrous* benzene was refluxed at 90 °C for 8 h. During the reaction, the benzene-water azeotrope was removed using Dean-Stark apparatus. The reaction mixture was then washed with saturated *aqueous* $NaHCO_3$ solution followed by saturated brine solution, and dried over *anhydrous* Na_2SO_4. Evaporation of the solvent followed by purification over silica gel column using 5% EtOAc in petroleum ether gave pure ketal **189** as colorless oil. Yield 417 mg, (83%); R_f 0.35 (10% EtOAc in petroleum ether); FT IR (neat) 1739 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.47-1.54 (m, 2H), 1.79-1.84 (m, 2H), 2.07 (q, J = 6.8 Hz, 2H), 2.66 (d, J = 1.9 Hz, 2H), 3.69 (d, J = 1.9 Hz, 3H), 3.94-4.00 (m, 4H), 4.95 (td, J =

10.3, 1.0 Hz, 1H), 5.01 (td, J = 17.1, 1.4 Hz, 1H), 5.74-5.85 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.69, 33.56, 37.04, 42.38, 51.66, 65.05, 109.22, 114.62, 138.42, 169.89; MS (ES): 215 (M^++1); Anal. Calcd. for $C_{11}H_{18}O_4$: C, 61.68; H, 8.41. Found: C, 61.42; H, 8.53.

(2-Pent-4-enyl-[1,3]dioxolan-2-yl)-acetic acid 190: A solution of 1*N* *aqueous* LiOH (13.0 mL, 13.0 mmol) was added drop-wise to a solution of methyl ester **189** (280 mg, 1.3 mmol) in THF (30 mL) and water (15 mL) mixture at 0 °C. The reaction mixture was then slowly warmed to rt and stirred for additional 8 h. It was again cooled to 0 °C, neutralized with 2*N* HCl and extracted with EtOAc. The combined organic layer was washed with saturated brine solution and dried over *anhydrous* Na_2SO_4. Evaporation of the solvent followed by purification over silica gel column using 30% EtOAc in petroleum ether gave the pure acid **190** as colorless oil. Yield 245 mg (94 %); R_f 0.50 (neat EtOAc); FT IR (neat) 3065-2894 (br), 1716 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.47-1.55 (m, 2H), 1.79-1.84 (m, 2H), 2.07 (bq, J = 7.3 Hz, 2H), 2.71 (s, 2H), 3.98-4.06 (m, 4H), 4.96 (dd, J = 10.2, 1.2 Hz, 1H), 5.01 (dd, J = 17.1, 1.5 Hz, 1H), 5.74-5.84 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.72, 33.53, 36.91, 42.30, 65.11, 109.19, 114.86, 138.29, 173.46; MS (ES): 201 (M^++1); Anal. Calcd. for $C_{10}H_{16}O_4$: C, 60.0, H, 8.0. Found: C, 59.83; H, 8.12.

(2-Pent-4-enyl-[1,3]dioxolan-2-yl)-acetic acid (1*R*)-methyl-prop-2-ynyl ester 191: A solution of (*S*)-3-butyn-2-ol (240 µL, 3.0 mmol) and PPh_3 (656 mg, 2.5 mmol) in *anhydrous* ether (3 mL) was added drop-wise to a solution of the acid **190** (500 mg, 2.5 mmol) and diisopropyl

azadicarboxylate (DIAD) (485 μL, 2.5 mmol) in *anhydrous* ether (3 mL) at 0 °C. After being stirred for 12 h at rt, the reaction mixture was filtered through a pad of celite to remove triphenylphosphine oxide and the filtrate was concentrated under vacuum to give crude material, which on purification over silica gel column using 5% EtOAc in petroleum ether gave pure ester **191** as colorless oil. Yield 420 mg (67%); R_f 0.50 (10% EtOAc in petroleum ether); $[\alpha]^{25}_D$ – 44.5 (*c* 1.15, $CHCl_3$); FT IR (neat) 3301, 2123, 1739 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.47-1.55 (m, 2H), 1.51 (d, J = 6.8 Hz, 3H), 1.79-1.84 (m, 2H), 2.07 (bq, J = 7.1 Hz, 2H), 2.45 (d, J = 2.2 Hz, 1H), 2.68 (s, 2H), 3.94-4.04 (m, 4H), 4.95 (dd, J = 10.2, 1.0 Hz, 1H), 5.01 (dd, J = 17.1, 1.4 Hz, 1H), 5.47 (dq, J = 6.6, 1.9 Hz, 1H), 5.75-5.85 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.13, 22.71, 33.59, 37.28, 42.54, 60.03, 65.13, 72.85, 81.94, 109.28, 114.70, 138.45, 168.26. Anal. Calcd. for $C_{14}H_{20}O_4$: C, 66.67; H, 7.94. Found: C, 66.73; H, 7.88.

(2-Pent-4-enyl-[1,3]dioxolan-2-yl)-acetic acid (1*R*)-methyl-allyl ester 192: Quinoline (1 mL of a stock solution [40 μL quinoline in 20 mL of hexane]) and the alkyne **191** (770 mg, 3.05 mmol) were dissolved in hexane (5 mL) and ethanol (5 mL) mixture. Commercially available Lindlar catalyst [$Pd/CaCO_3$] (100 mg) was added to it and the resulting suspension was stirred for 1 h under an atmosphere of H_2 (1 atm). The catalyst was filtered off through a pad of celite, solvent was evaporated and the residue was purified over silica gel column using 5% EtOAc in petroleum ether to give pure diene **192** as colorless oil. Yield 700 mg (90%); R_f 0.30 (10% EtOAc in petroleum ether); $[\alpha]^{25}_D$

−14.70 (*c* 1.05, $CHCl_3$); FT IR (neat) 1735 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.32 (d, J = 6.3 Hz, 3H), 1.47-1.55 (m, 2H), 1.79-1.84 (m, 2H), 2.07 (bq, J = 7.3 Hz, 2H), 2.65 (s, 2H), 3.94-4.02 (m, 4H), 4.95 (qd, J = 10.3, 1.2 Hz, 1H), 5.01 (qd, J = 17.3, 1.7 Hz, 1H), 5.14 (td, J = 10.5, 1.2 Hz, 1H), 5.27 (td, J = 17.3, 1.5 Hz, 1H), 5.34-5.41 (m, 1H), 5.75-5.89 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.83, 22.74, 33.64, 37.19, 42.79, 65.05, 71.08, 109.35, 114.66, 115.85, 137.49, 138.49, 168.68; MS (ES): 255 (M^++1); Anal. Calcd. for $C_{14}H_{22}O_4$: C, 66.14; H, 8.66. Found: C, 66.39; H, 8.65.

(9*R*)-Methyl-1,4,8-trioxa-spiro[4.9]tetradecan-7-one 194: A solution of ruthenium carbene **II** (167 mg, 0.197 mmol) in *anhydrous* benzene (100 mL) was added drop-wise to a solution of diene **192** (500 mg, 1.97 mmol) in *anhydrous* benzene (100 mL) at 80 °C over a period of 4 h. After being stirred for additional 6 h at reflux temperature, the solvent was evaporated and the crude material was filtered through a pad of silica gel. The solvent was removed under reduced pressure and the residue (435 mg) was redissolved in EtOH (30 mL) and taken in a hydrogenation flask. Pd/C (80 mg) was added to it. The reaction flask was then fixed in hydrogenation apparatus and hydrogenated under H_2 pressure (30 psi) for 8 h. It was filtered and washed with EtOH. The solvent was removed under reduced pressure and the crude residue on purification over silica gel column using 25% EtOAc in petroleum ether gave pure macrolactone **19** as viscous liquid. Yield 395 mg (88 %); R_f 0.65 (40% EtOAc in petroleum ether); $[\alpha]^{25}_D$ + 4.29 (*c* 0.70, $CHCl_3$); FT IR (neat) 1730 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.21 (d,

J = 6.1 Hz, 3H), 1.24-1.59 (m, 8H), 1.71-1.80 (m, 2H), 2.56-2.66 (m, 2H), 3.95-3.99 (m, 4H), 4.95-4.98 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.86, 24.02, 24.80, 29.78, 35.75, 37.08, 42.50, 64.62, 64.90, 70.90, 109.19, 169.04; MS (FAB): 229 (M^++1); Anal. Calcd. for $C_{12}H_{20}O_4$: C, 63.16; H, 8.77. Found: C, 63.11; H, 8.49.

(9*R*)-3-Oxodecan-9-olide 195.[101] *p*-TSA (20 mg, 0.11 mmol) was added to a solution of the acetal **194** (120 mg, 0.52 mmol) in wet acetone (3 mL) at room temperature. After being stirred for 6 h at rt, the solvent was evaporated and the residue was directly loaded on a silica gel column and chromatographed using 20% EtOAc in petroleum ether to give β-ketolactone **195** as low melting solid. Yield 88 mg (91 %); R_f 0.65 (40% EtOAc in petroleum ether); $[\alpha]^{25}_D$ +34.0 (*c* 1, $CHCl_3$); FT IR (KBr) 1734, 1644 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.23 (d, J = 6.4 Hz, 3H), 1.26-1.33 (m, 4H), 1.50-1.69 (m, 4H), 2.45-2.63 (m, 2H), 3.41 (s, 2H), 4.93-5.01 (m, 1H); MS (FAB): 185 (M^++1); Anal. Calcd. for $C_{10}H_{16}O_3$: C, 65.22; H, 8.70. Found: C, 65.46; H, 8.62.

***O-tert*-butyl dimethyl silyl-*N*-benzyloxy carbonyl (*L*)-threonine 201:**[112b] A solution of TBDMS-Cl (3.1 g, 20.4 mmol) in *anhydrous* DMF (5 mL) was added drop-wise to a solution of *N*-cbz-*L*-threonine[124] (**200**) (4.3 g, 17.0 mmol) and imidazole (2.3 g, 34.0 mmol) in *anhydrous* DMF (10 mL) at 0 °C. The resulting solution was slowly warmed to rt and stirred for 12 h. The reaction mixture was diluted with water (15 mL) and extracted with EtOAc. The combined organic layer was washed with saturated brine solution and dried over *anhydrous* Na_2SO_4. Evaporation of the solvent followed by purification over silica

gel column using 50% EtOAc in petroleum ether gave pure product **201**. Yield 3.8 g (61%); White solid. mp 156-158 °C (lit[112b] 154-157 °C); R_f 0.45 (50% ethyl acetate in petroleum ether); $[\alpha]^{25}_D$ +10.3 (*c* 1, $CHCl_3$) {lit[112b] $[\alpha]^{22}_D$ +10.5 (*c* 1.69, $CHCl_3$)}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.09 (s, 3H), 0.10 (s, 3H), 0.87 (s, 9H), 1.21 (d, J = 6.4 Hz, 3H), 4.33 (dd, J = 8.1, 2.5 Hz, 1H), 4.48 (dq, J = 6.1, 2.4 Hz, 1H), 5.14 (s, 2H), 5.53 (bd, J = 8.0 Hz, 1H, *NH*), 7.33-7.38 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ –5.26, –4.62, 17.83, 19.63, 25.61, 59.21, 67.25, 68.45, 128.14, 128.27, 128.57, 136.29, 156.49, 173.93.

(2*S*,3*R*,1*S*)-2-Benzyloxycarbonylamino-3-(*t*-butyl-dimethyl-silanyl)-butyric acid 1-methyl-prop-2-ynyl ester 202: A solution of DCC (1.24 g, 6.0 mmol) in *anhydrous* CH_2Cl_2 (5 mL) was added drop-wise to a solution (*S*)-3-bytyn-2-ol (520 µL, 6.56 mmol), acid **201** (2.0 g, 5.46 mmol) and 4-DMAP (668 mg, 5.46 mmol) in *anhydrous* CH_2Cl_2 (15 mL) at 0 °C . The resulting suspension was slowly warmed to rt and stirred for 12 h. The reaction mixture was then filtered through a pad of celite and the filtrate was washed with water, saturated brine solution and dried over *anhydrous* Na_2SO_4. Evaporation of the solvent gave crude material, which on purification over silica gel column using 5% EtOAc in petroleum ether gave pure ester **202**. Yield 1.62 g (71 %); colorless gel; R_f 0.50 (10% EtOAc in petroleum ether); FT IR (film) 3446, 3303, 2124, 1732 cm^{-1}; $[\alpha]^{25}_D$ +24.5 (*c* 1, $CDCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ –0.04 (s, 3H), 0.00 (s, 3H), 0.79 (s, 9H), 1.17 (d, J = 6.4 Hz, 3H), 1.46 (d, J = 6.8 Hz, 3H), 2.41 (d, J = 4.0 Hz, 1H), 4.24 (dd, J = 9.8 Hz, 1H), 4.40 (dq, J = 6.1, 1.7 Hz, 1H), 5.1 (d, J = 1.5, 2H),

5.35-5.42 (m, 2H), 7.21-7.36 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ – 5.22, -4.24, 17.81, 20.85, 21.17, 25.66, 59.95, 61.16, 67.07, 68.67, 73.52, 81.50, 127.88, 128.09, 128.15, 128.52, 136.24, 156.63, 169.79. MS (FAB): 420 (M^++1). Anal. Calcd. for $C_{22}H_{33}NO_5Si$: C, 63.01; H, 7.88; N, 3.34. Found: C, 62.89; H, 7.83; N, 3.29.

(2*S*,3*R*,1*S*)-2-Benzyloxycarbonylamino-3-hydroxy-butyric acid 1 methyl-prop-2-ynyl ester 203: TBAF (1M solution in THF with 5% water) (5.4 mL, 5.4 mmol) was added to a solution of silyl ether **202** (1.5 g, 3.6 mmol) in *anhydrous* THF (10 mL) at 0 °C. After being stirred for 8 h at rt, the reaction mixture was quenched by adding saturated NH_4Cl solution and extracted with EtOAc. The combined organic layer was washed with saturated brine solution and dried over *anhydrous* Na_2SO_4. Evaporation of the solvent followed by purification over silica gel column using 30% EtOAc in petroleum ether gave pure alcohol **203**. Yield 670 mg (61%); Colorless oil; R_f 0.70 (50% EtOAc in petroleum ether); $[\alpha]^{25}_D$ +24.7 (*c* 1.9, $CHCl_3$); FT IR (film) 3419 (br), 3299, 2123, 1728 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.25 (d, J = 6.4 Hz, 3H), 1.51 (d, J = 6.8 Hz, 3H), 2.48 (d, J = 1.8 Hz, 1H), 4.34-4.36 (m, 2H), 5.13 (s, 2H), 5.49 (bq, J = 6.4 Hz, 1H), 5.63 (bd, J = 7.6 Hz, 1H) 7.29-7.37 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.95, 21.05, 59.16, 61.49, 67.19, 68.14, 73.68, 81.31, 128.02, 128.18, 128.52, 136.10, 156.65, 169.95; MS (FAB): 306 (M^++1). $C_{16}H_{19}NO_5$: C, 62.95; H, 6.23; N, 4.59. Found: C, 62.91; H, 5.99; N, 4.58.

(2*S*,3*R*,1*S*)-2-Benzyloxycarbonylamino-3-hydroxy-butyric acid 1-methyl-allyl ester 204: Quinoline (400 μL [A stock solution prepared

by dissolving 40 μL of quinoline in 20 mL hexane]) was added to a suspension of alkyne **203** (500 mg, 1.64 mmol) and commercially available Lindlar catalyst $Pd/CaCO_3$ (100 mg) in EtOH (5 mL) and hexane (5 mL) mixture at rt and stirred for 4 h under an atmosphere of H_2 (1 atm). It was filtered through a pad of celite, solvent was evaporated on rotary evaporator and the residue on purification over silica gel using 20% EtOAc in petroleum ether gave pure alkene **204**. Yield 440 mg (87%). Colorless oil; R_f 0.50 (30% EtOAc in petroleum ether); $[\alpha]^{25}_D$ – 4.5 (*c* 2, $CHCl_3$); FT IR (film) 3424 (br), 1721 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.25 (d, J = 6.4 Hz, 3H), 1.33 (d, J = 6.6 Hz, 3H), 1.98 (bs, 1H), 4.31- 4.33 (m, 2H), 5.13 (s, 2H), 5.15 (d, J = 10.8 Hz, 1H), 5.27 (d, J = 17.3 Hz, 1H), 5.41 (quintet, J = 6.4 Hz, 1H), 5.57 (bs, 1H), 5.79-5.87 (m, 1H), 7.30-7.37 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.79, 19.94, 59.18, 67.16, 68.18, 72.66, 116.53, 128.04, 128.19, 128.53, 136.17, 136.84,157.82, 170.32; MS (FAB): 308 (M^++1). Anal. Calcd. for $C_{16}H_{21}NO_5$: C, 62.54; H, 6.84; N, 4.56. Found: C, 62.53; H, 6.52; N, 4.49.

(3*R*,2*S*,1*S*)-3-Acryloyloxy-2-benzyloxycarbonylamino-butyric acid 1-methyl-allyl ester 198: Acryloyl chloride (70 μL, 0.85 mmol) was added in a drop-wise manner to a solution of hydroxy ester **204** (200 mg, 0.65 mmol) and Et_3N (136 μL, 0.98 mmol) in *anhydrous* CH_2Cl_2 at 0 °C and the resulting solution was stirred at RT for 6 h. The reaction mixture was diluted with CH_2Cl_2, washed with 0.1 *N* aq HCl solution, water, saturated brine solution and dried over *anhydrous* Na_2SO_4. Evaporation of the solvent followed by purification over silica

gel column using 5% EtOAc in petroleum ether gave pure product **198** as a colorless oil. Yield 157 mg (67%); R_f 0.5 (20% EtOAc in petroleum ether); FT IR (neat) 3423, 1743, 1719 cm^{-1}; $[\alpha]^{25}_D$ +17.8 (*c* 0.55, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 1.26 (d, J = 6.6 Hz, 3H), 1.34 (d, J = 6.4 Hz, 3H), 4.54 (dd, J = 9.6, 2.4 Hz, 1H), 5.10 (d, J = 10.4 Hz, 1H), 5.15 (s, 2H), 5.20 (d, J = 17.2 Hz, 1H), 5.35 (quintet, J = 6.8 Hz, 1H), 5.48-5.50 (m, 2H), 5.69-5.77 (m, 1H), 5.81 (d, J = 10.8 Hz, 1H), 6.02 (dd, J = 17.2, 10.4 Hz, 1H), 6.35 (d, J = 17.2, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.84, 19.75, 57.86, 67.36, 70.88, 72.99, 116.93, 127.88, 128.17, 128.31, 128.59, 131.48, 136.07, 136.69, 156.55, 164.72, 168.94; MS (FAB): 362 (M^++1).

Cyclization of 198. A solution of ruthenium carbene (12 mg, 0.014 mmol) in *anhydrous* benzene (20 mL) was added drop-wise manner to a solution of diene ester **198** (50 mg, 0.14 mmol) in *anhydrous* benzene (50 mL) at 80 °C over a period of 1.5 h. After being stirred for further 6.5 h, the reaction mixture was cooled to rt. The solvent was evaporated in *vacuo* and the crude material was purified through silica gel column using 10-20% EtOAc in petroleum ether to give the cyclized products *cis*-**197** and *trans*-**197**. Yield 37 mg (80 %).

***cis*-197:** 18 mg; white solid; 118-120 °C; R_f 0.6 (40% EtOAc in petroleum ether); $[\alpha]^{25}_D$ +2.6 (*c* 0.5, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 1.26 (d, J = 6.1 Hz, 3H), 1.34 (d, J = 6.3 Hz, 3H), 4.61 (dd, J = 9.0, 2.2 Hz, 1H), 5.13-5.15 (m, 2H), 5.28-5.30 (m, 1H), 5.39-5.42 (m, 2H), 5.62 (bdd, J = 3.9, 1.2 Hz, 1H), 6.70 (s, 1H), 7.36-7.40 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.70, 20.52, 57.54, 67.44, 71.56,

72.57, 128.26, 128.40, 128.60, 130.71, 133.46, 135.87, 155.96, 163.19, 168.42.

***Trans*-197:** 19 mg; Viscous paste; R_f 0.55 (40% EtOAc in petroleum ether); $[\alpha]^{25}_D$ –18.4 (*c* 0.25, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 1.30 (d, J = 6.8 Hz, 3H), 1.38 (d, J = 6.1 Hz, 3H), 4.59 (d, J = 10.0 Hz, 1H), 5.18 (AB q, J = 12.0 Hz, 2H), 5.47-5.52 (m, 2H), 5.65-5.67 (m, 1H), 5.73 (dd, J = 15.4, 1.5 Hz, 1H), 6.92 (dd, J = 15.4, 2.9 Hz, 1H), 7.36-7.38 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.61, 19.62, 58.49, 67.55, 69.46, 71.71, 85.39, 117.73, 128.17, 128.31, 128.51, 128.67, 135.94, 148.15, 164.17.

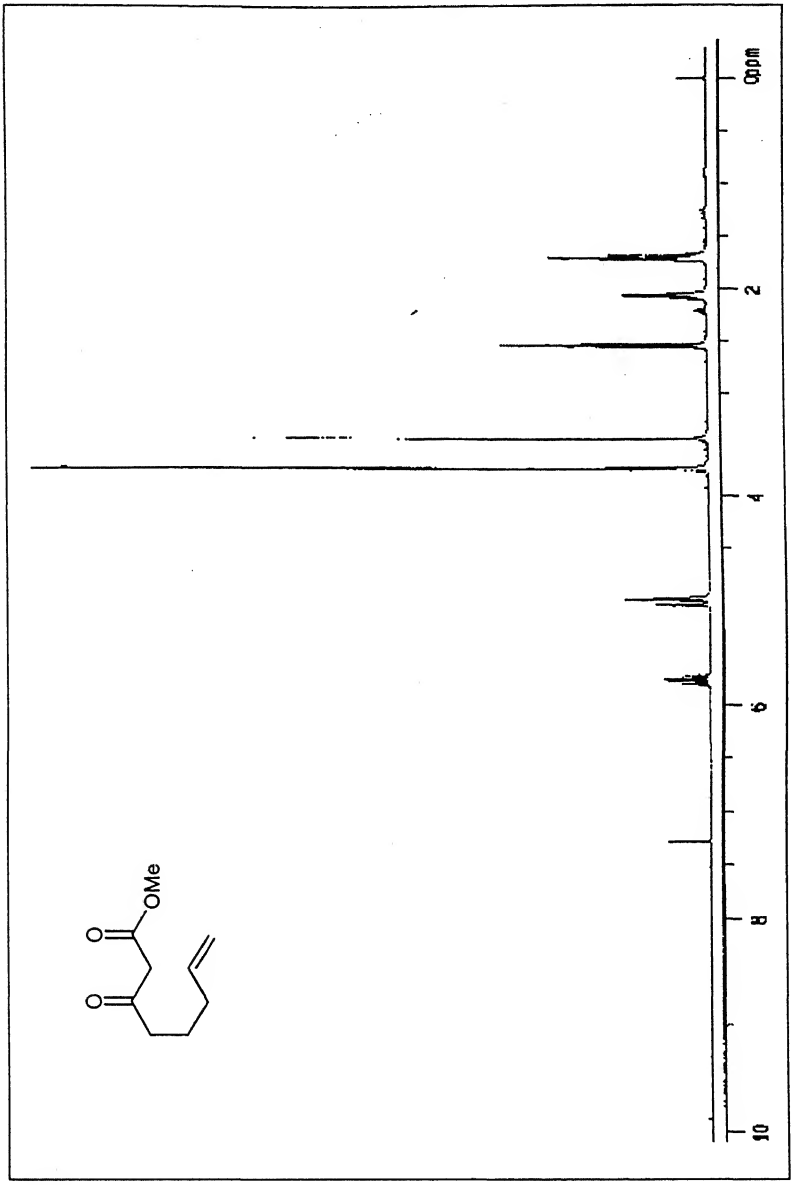


Figure 3.1 ^{1}H NMR spectrum of **182**

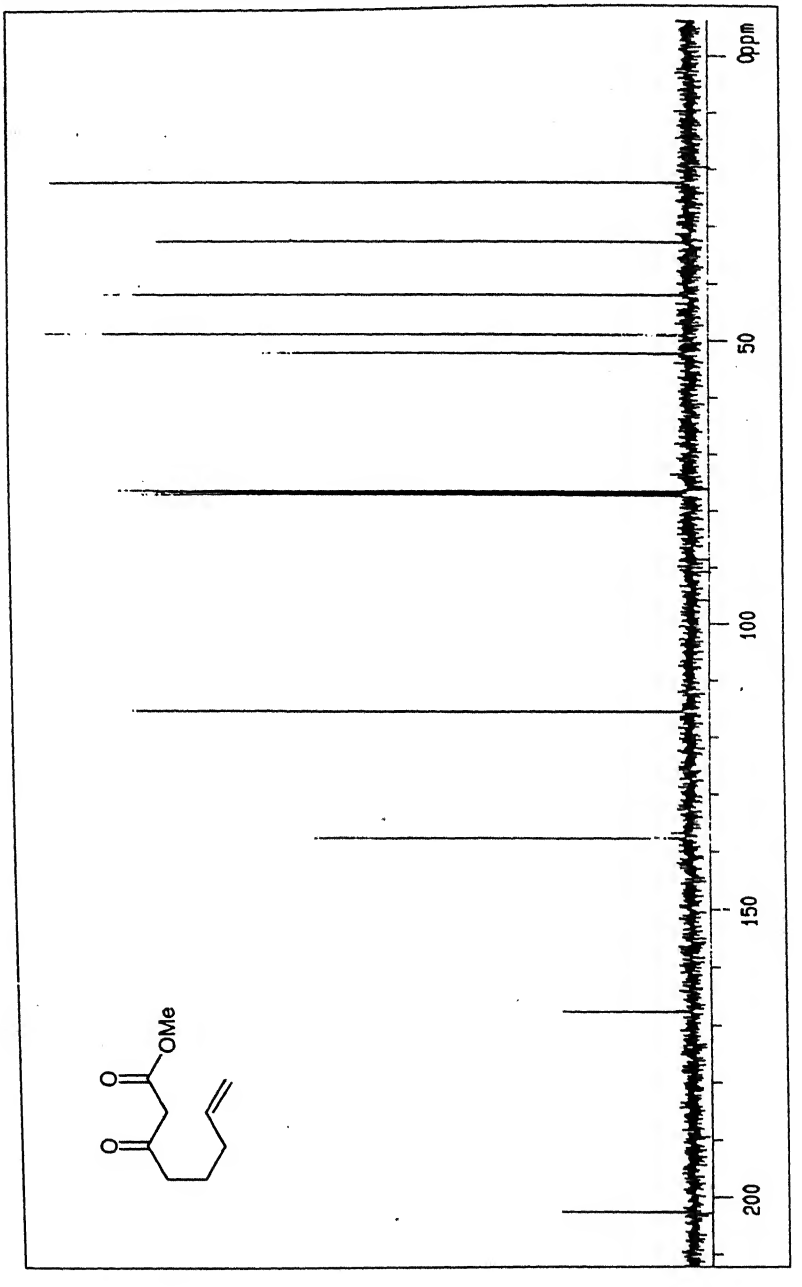


Figure 3.2 ^{13}C NMR spectrum of **182**

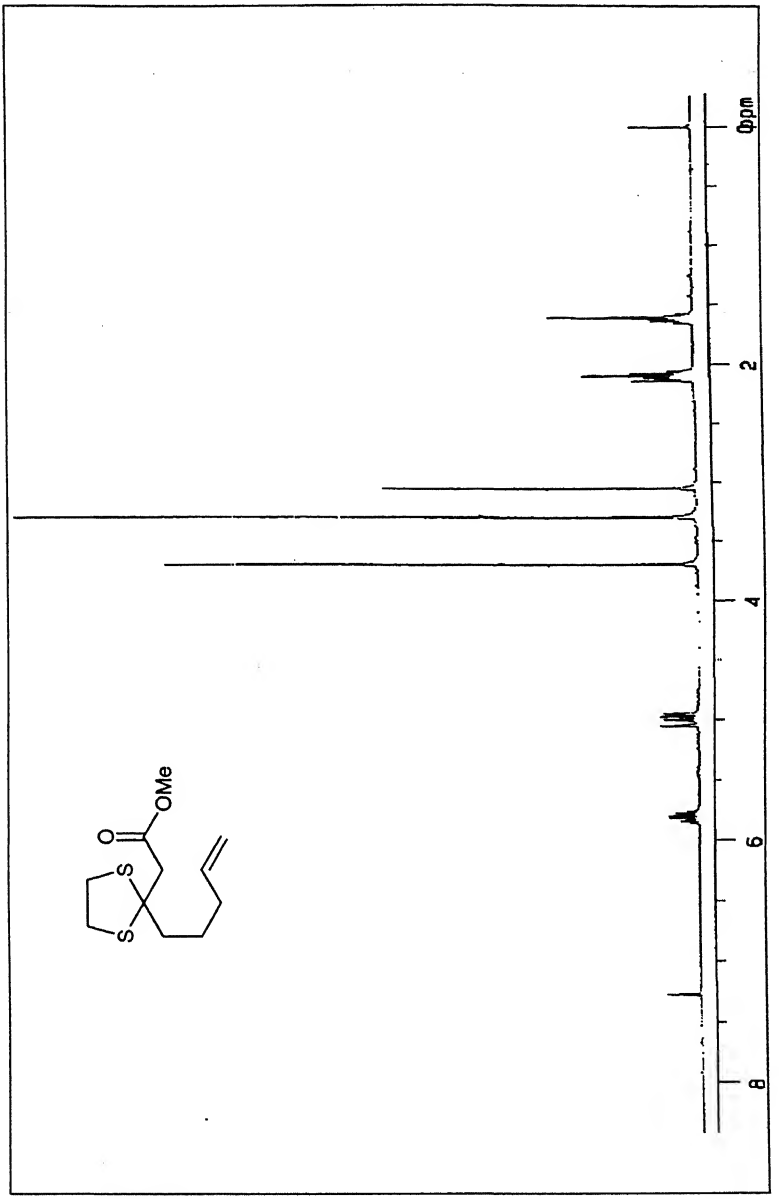


Figure 3.3 ^{1}H NMR spectrum of **183**

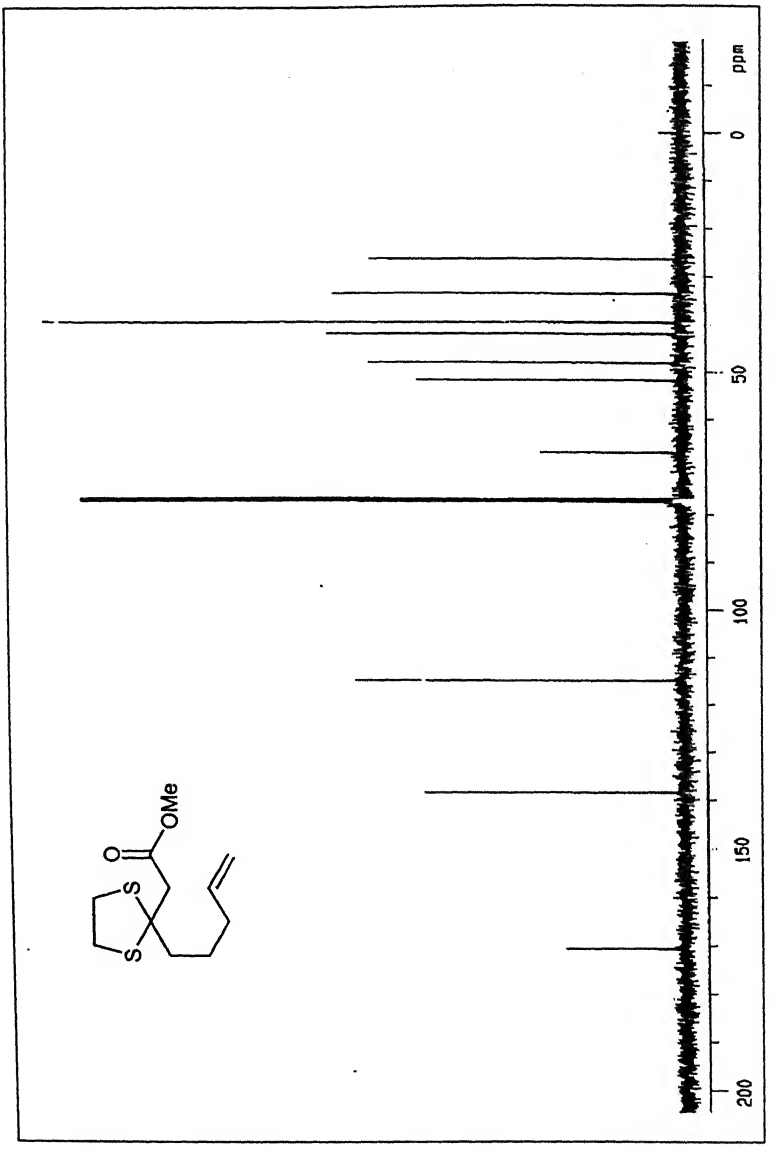


Figure 3.4 ^{13}C NMR spectrum of **183**

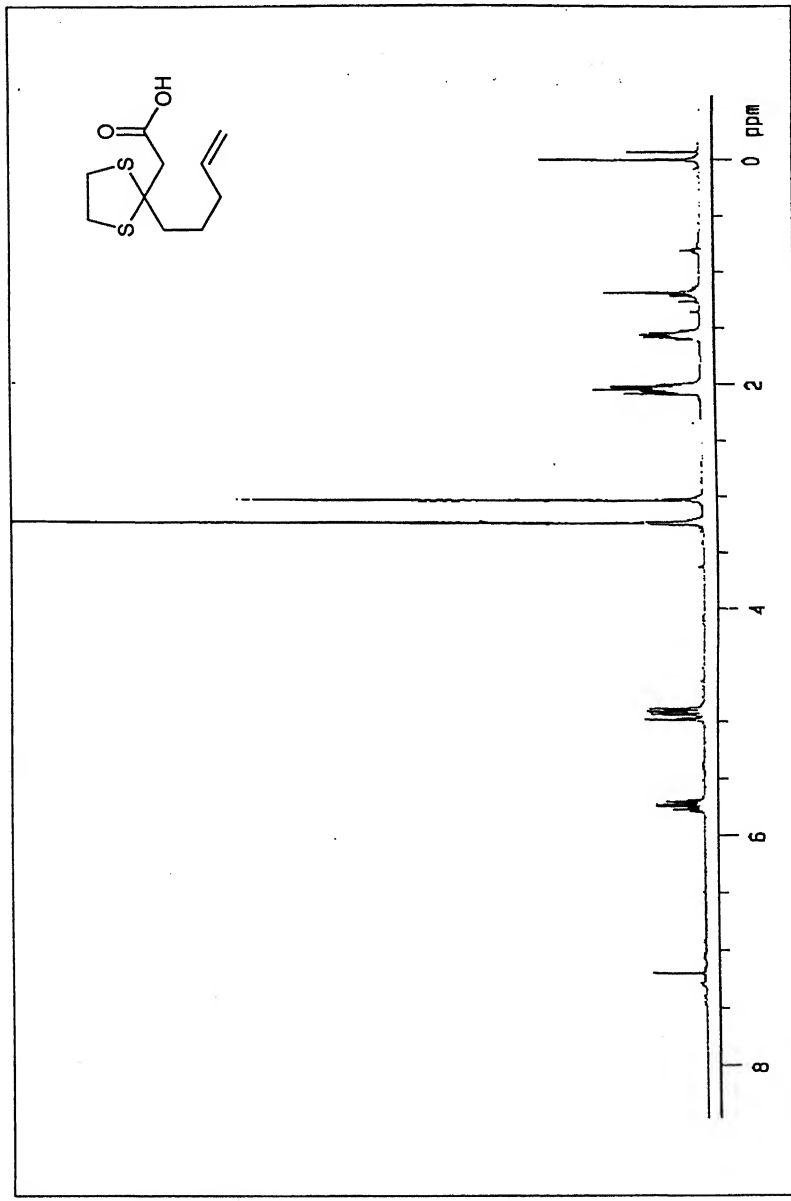


Figure 3.5 ^{1}H NMR spectrum of **184**

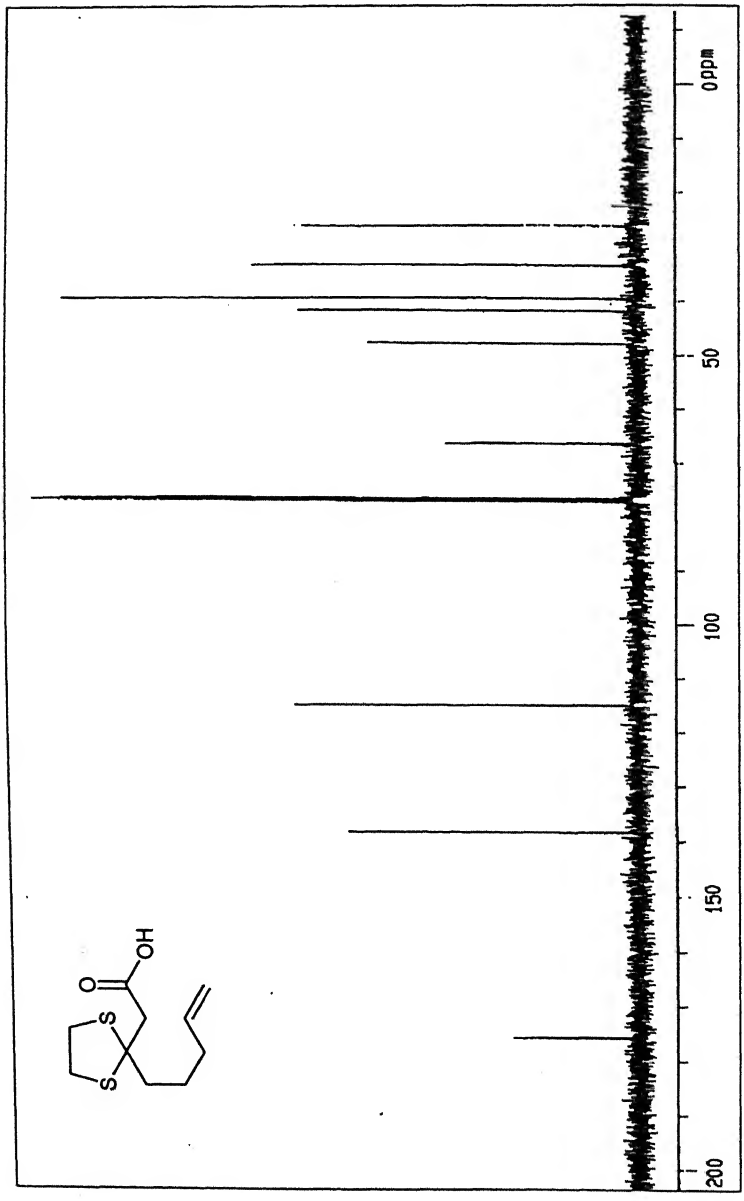


Figure 3.6 ^{13}C NMR spectrum of **184**

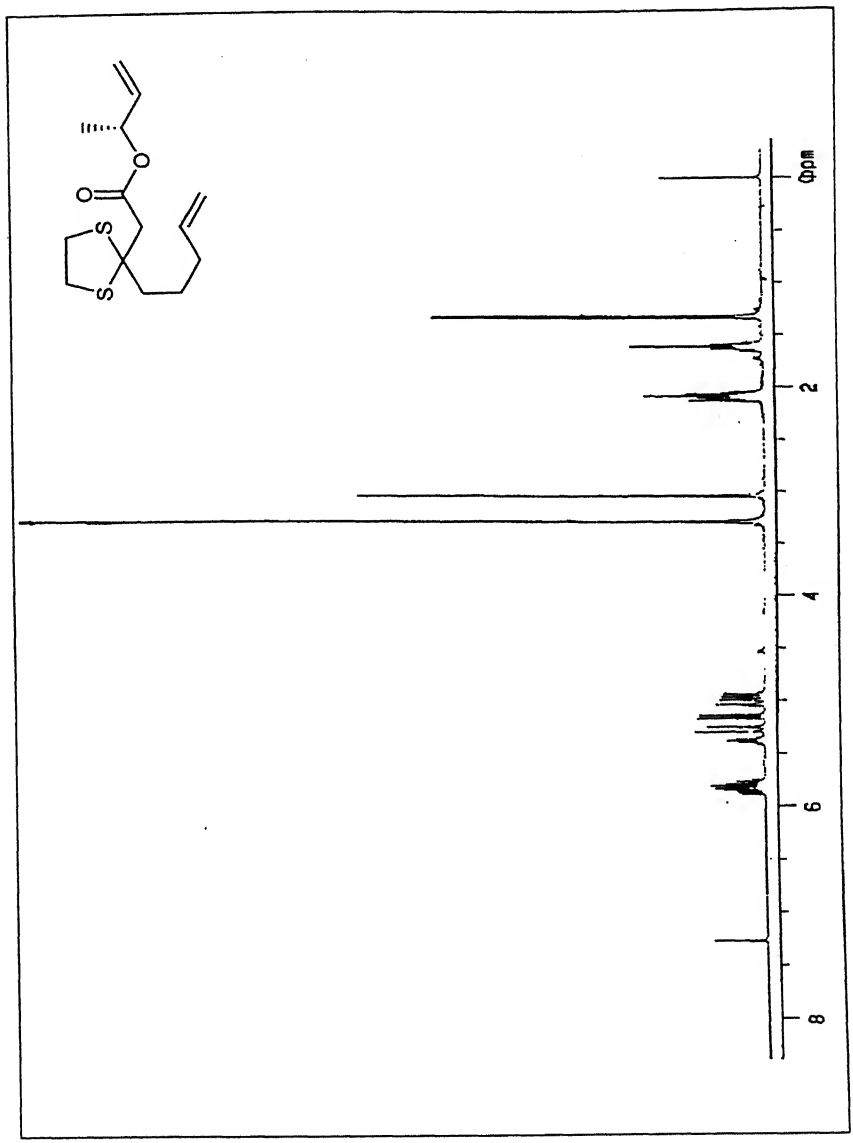


Figure 3.7 ^{1}H NMR spectrum of **185**

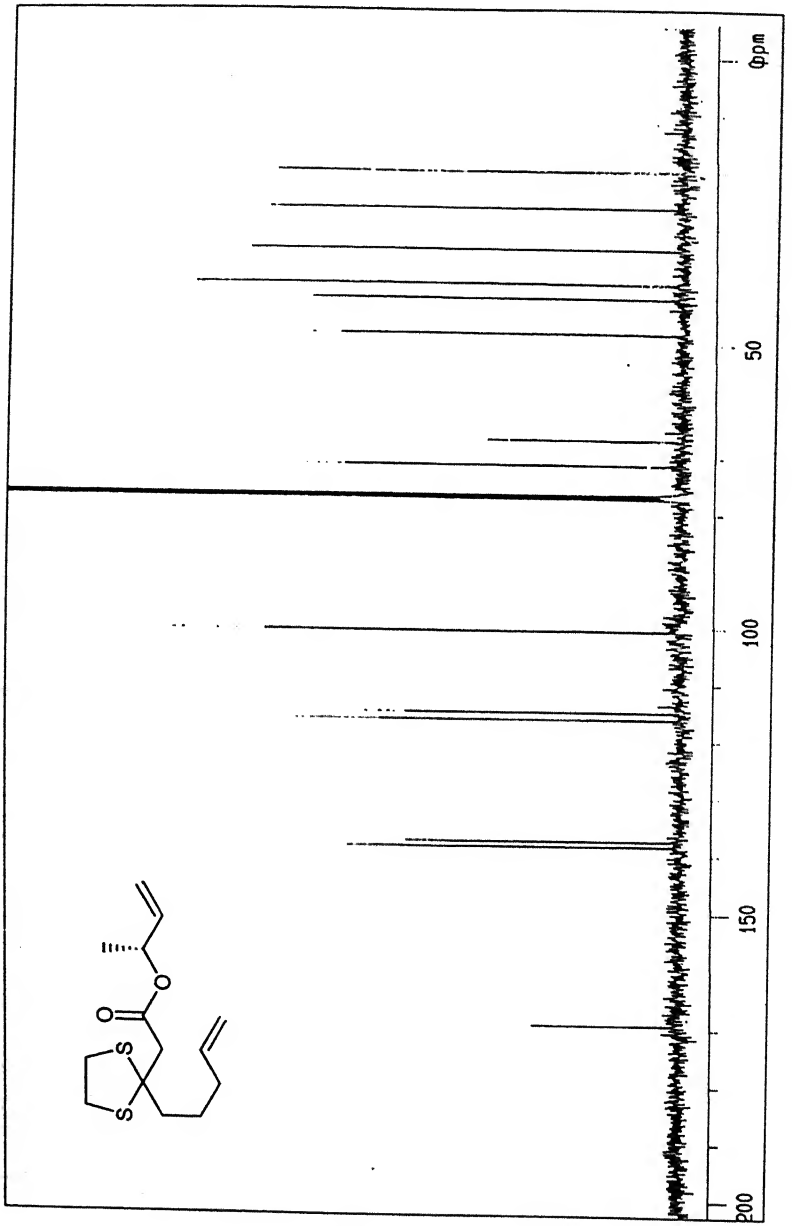


Figure 3.8 ^{13}C NMR spectrum of **185**

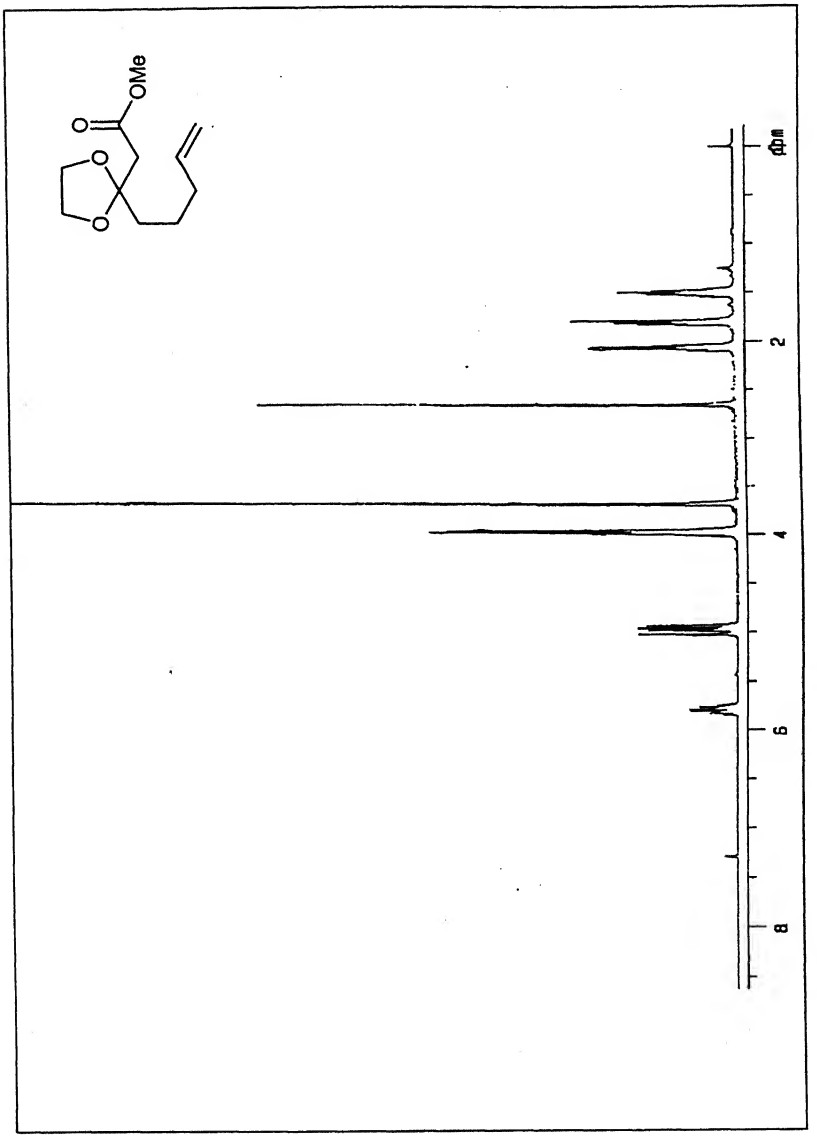


Figure 3.9 ^{1}H NMR spectrum of **189**

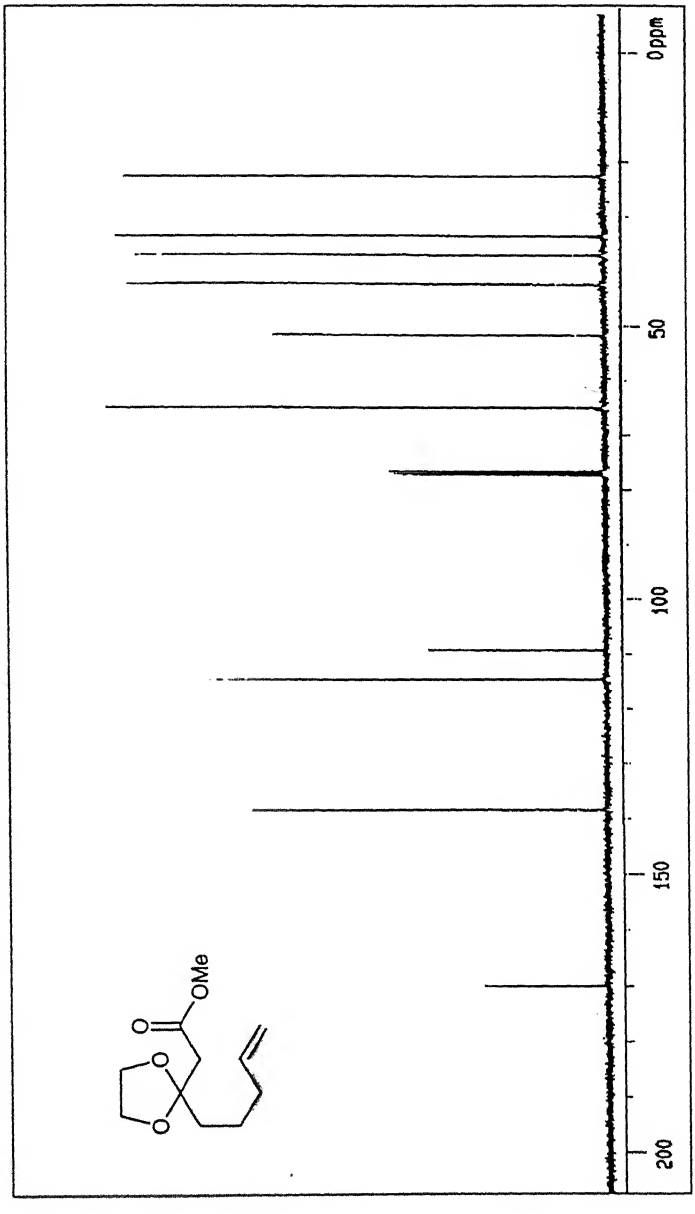


Figure 3.10 ^{13}C NMR spectrum of **185**

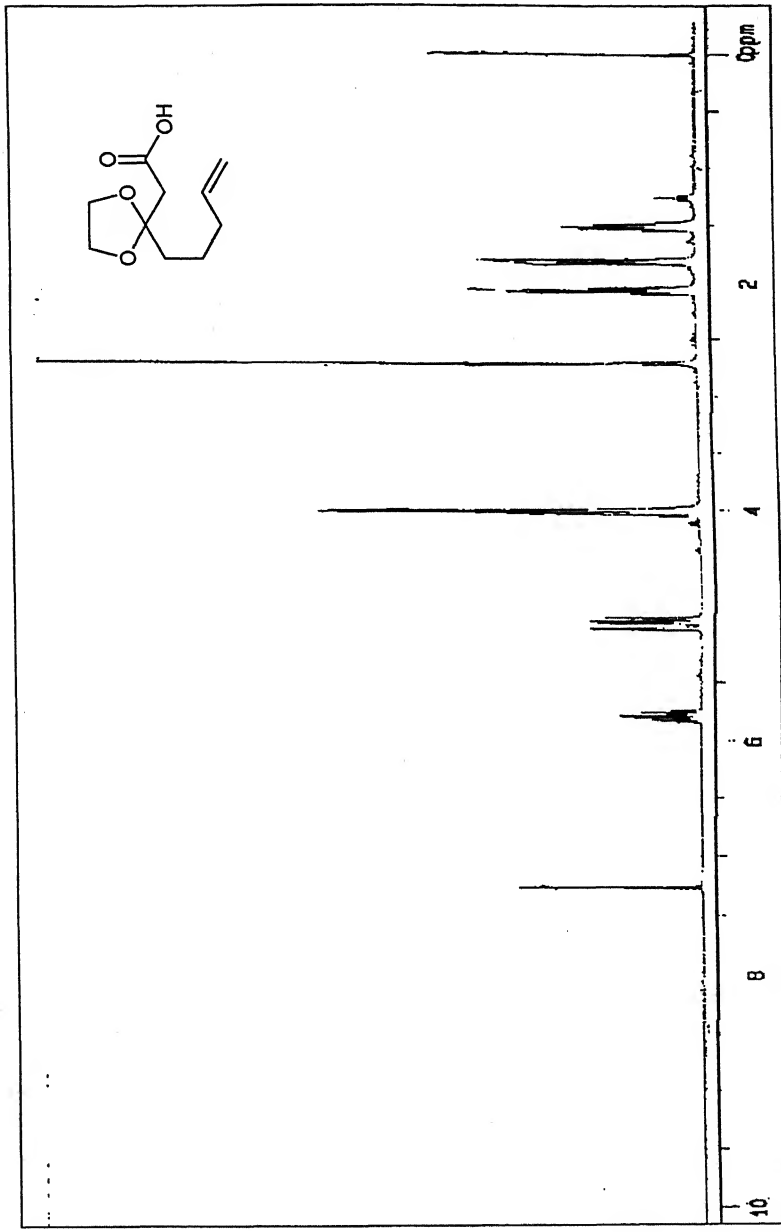


Figure 3.11 ^{1}H NMR spectrum of **190**

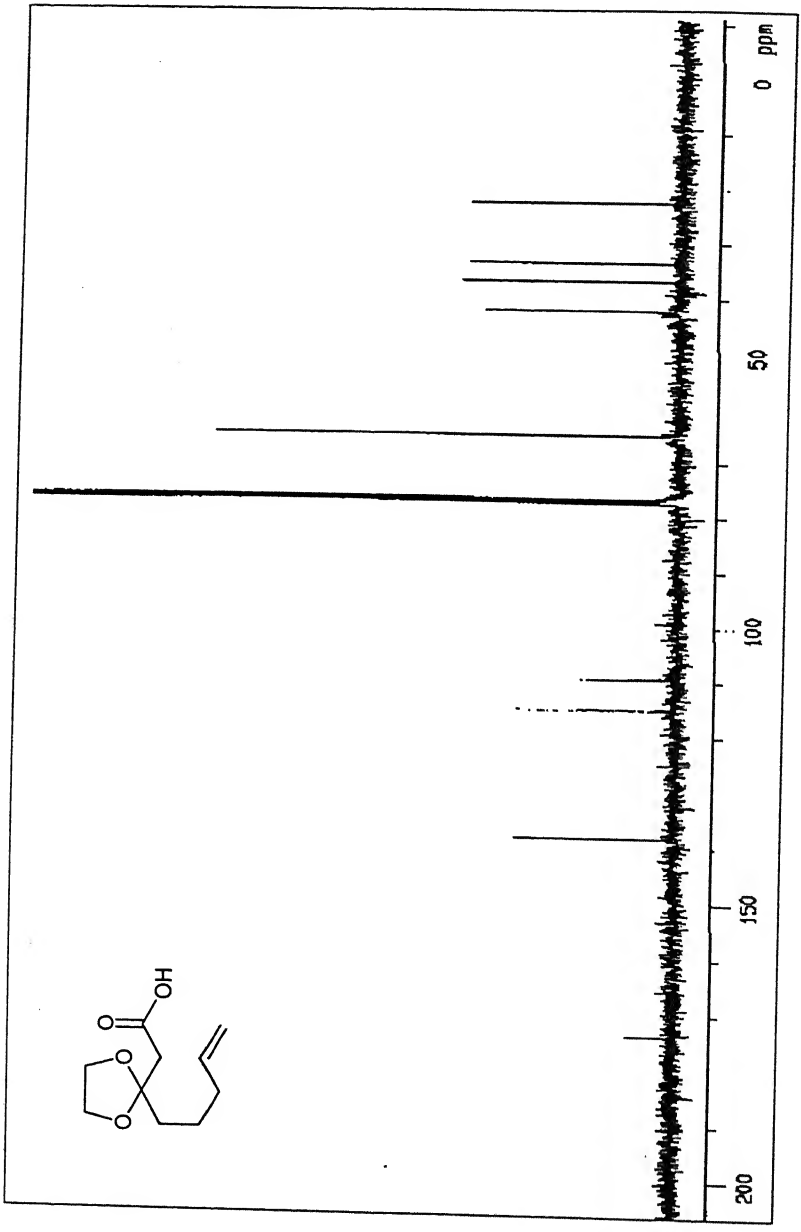


Figure 3.12 ^{13}C NMR spectrum of **190**

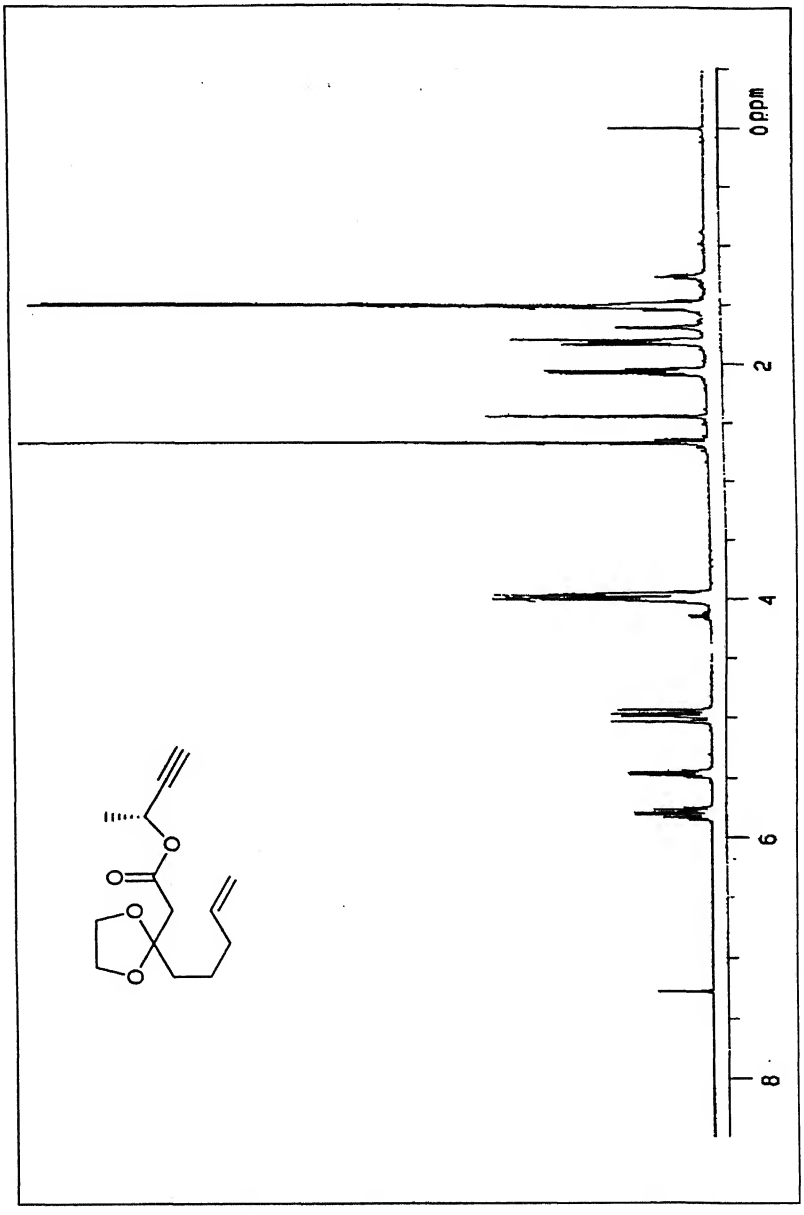


Figure 3.13 ^{1}H NMR spectrum of **191**

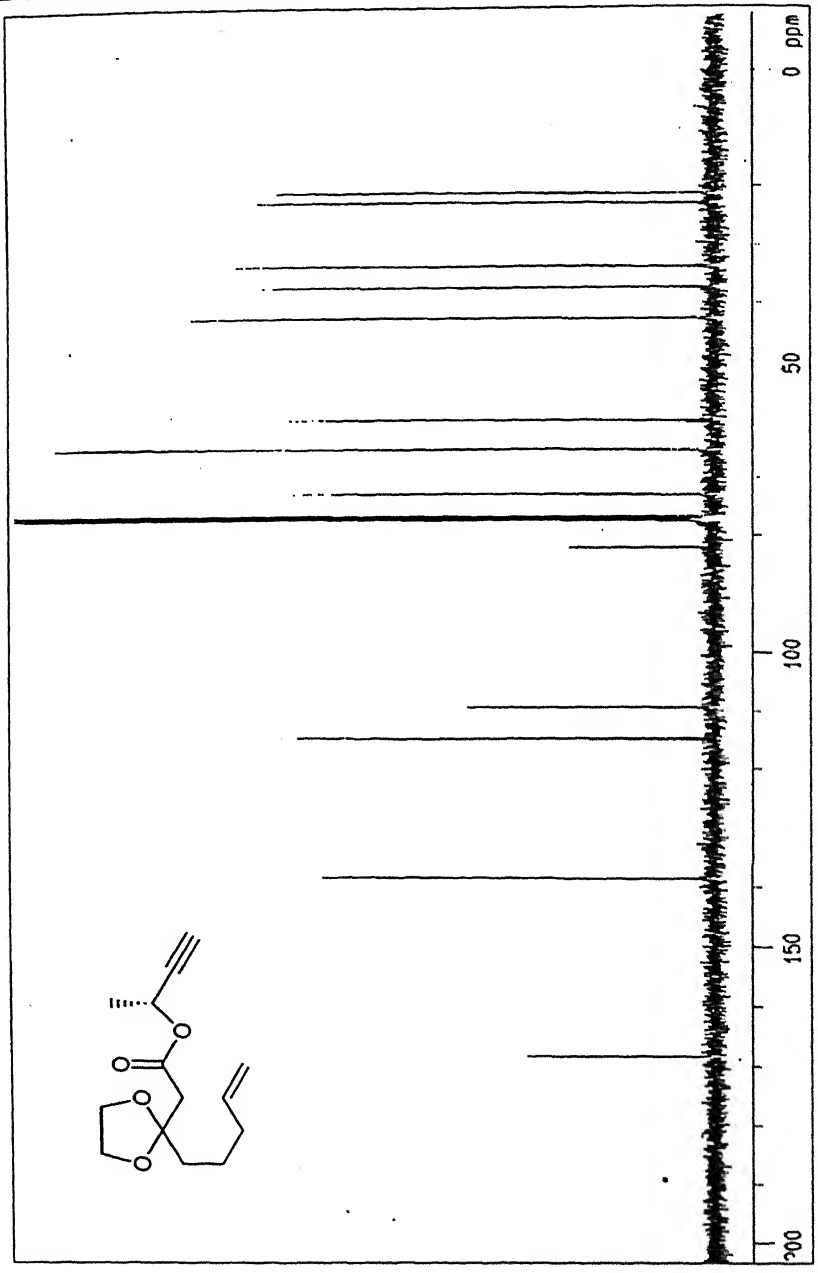


Figure 3.14 ^{13}C NMR spectrum of **191**

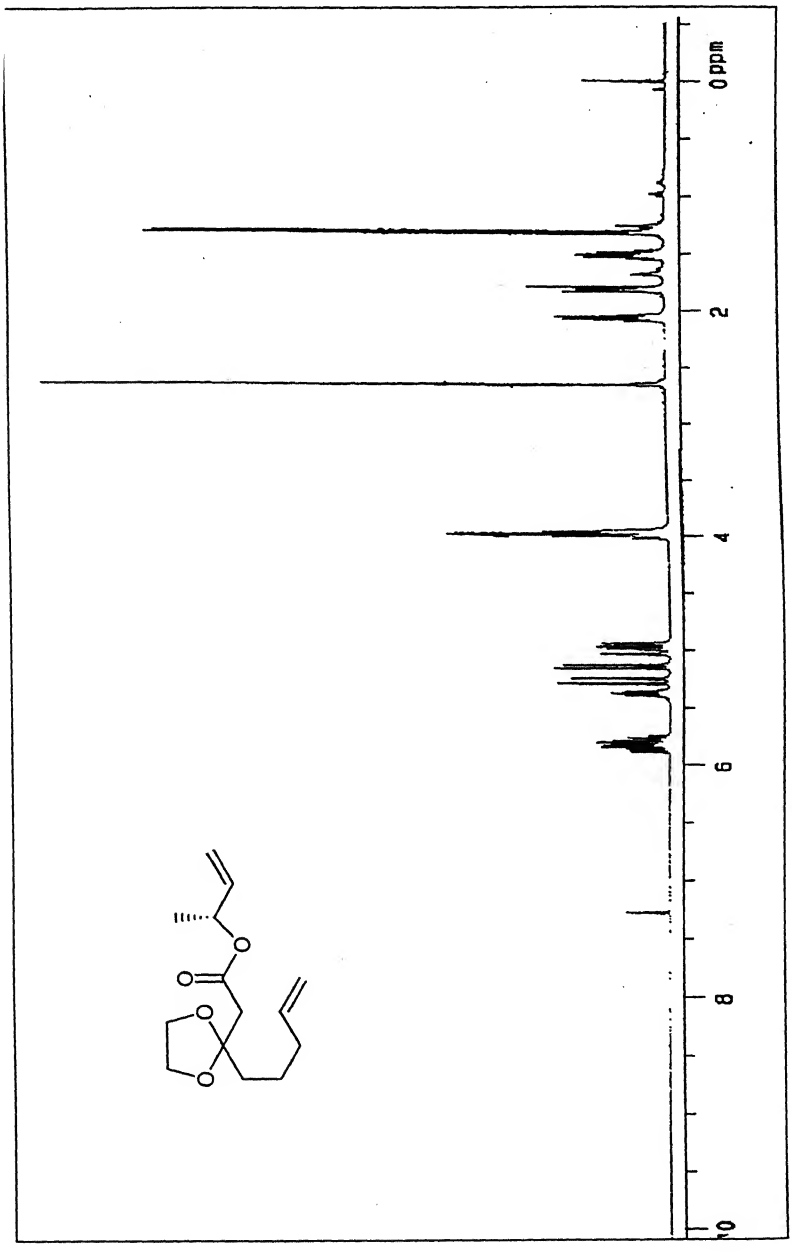


Figure 3.15 ^{1}H NMR spectrum of **192**

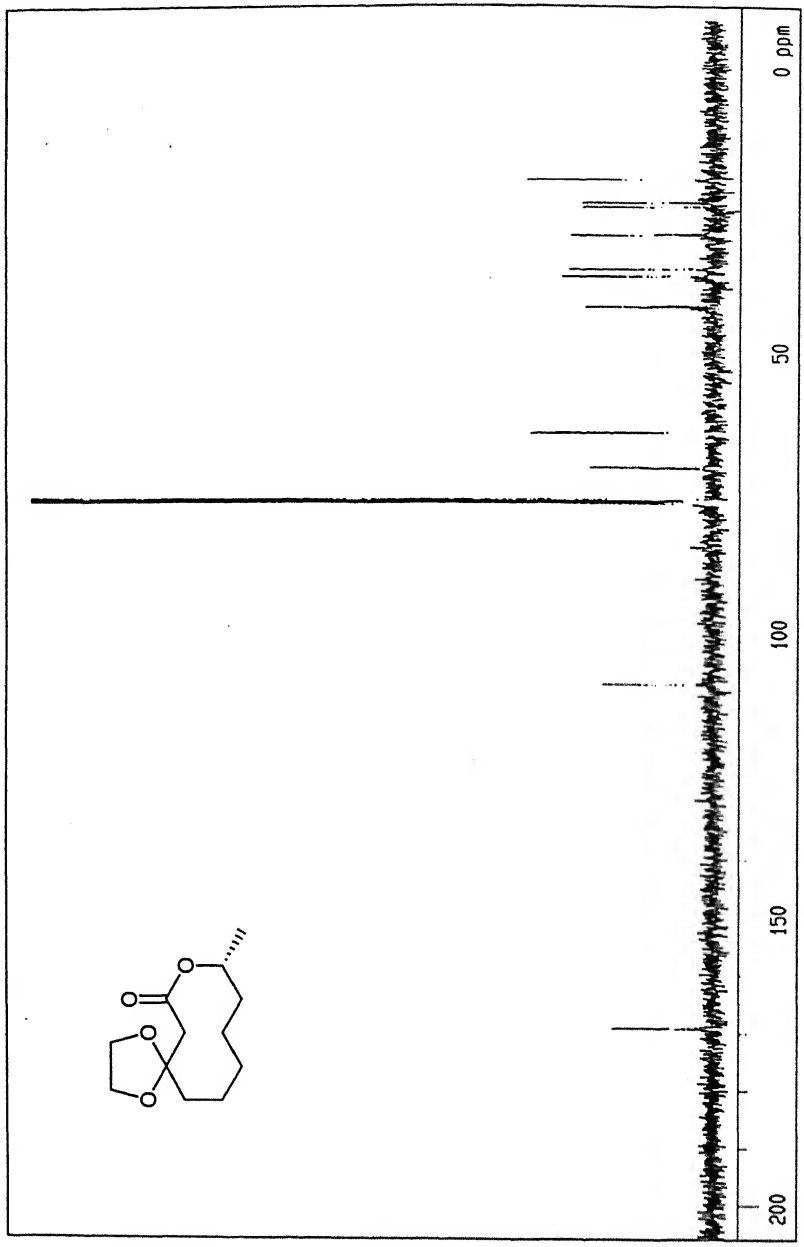


Figure 3.16 ^{13}C NMR spectrum of **192**

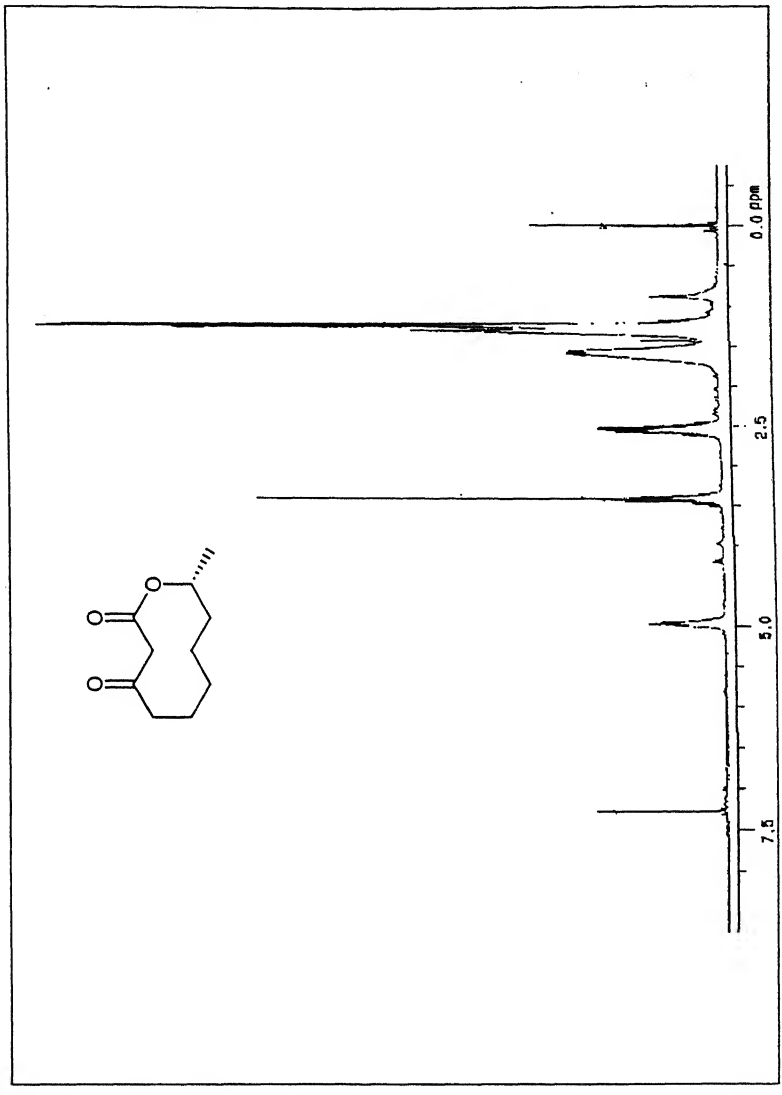


Figure 3.19 ^{1}H NMR spectrum of **195**

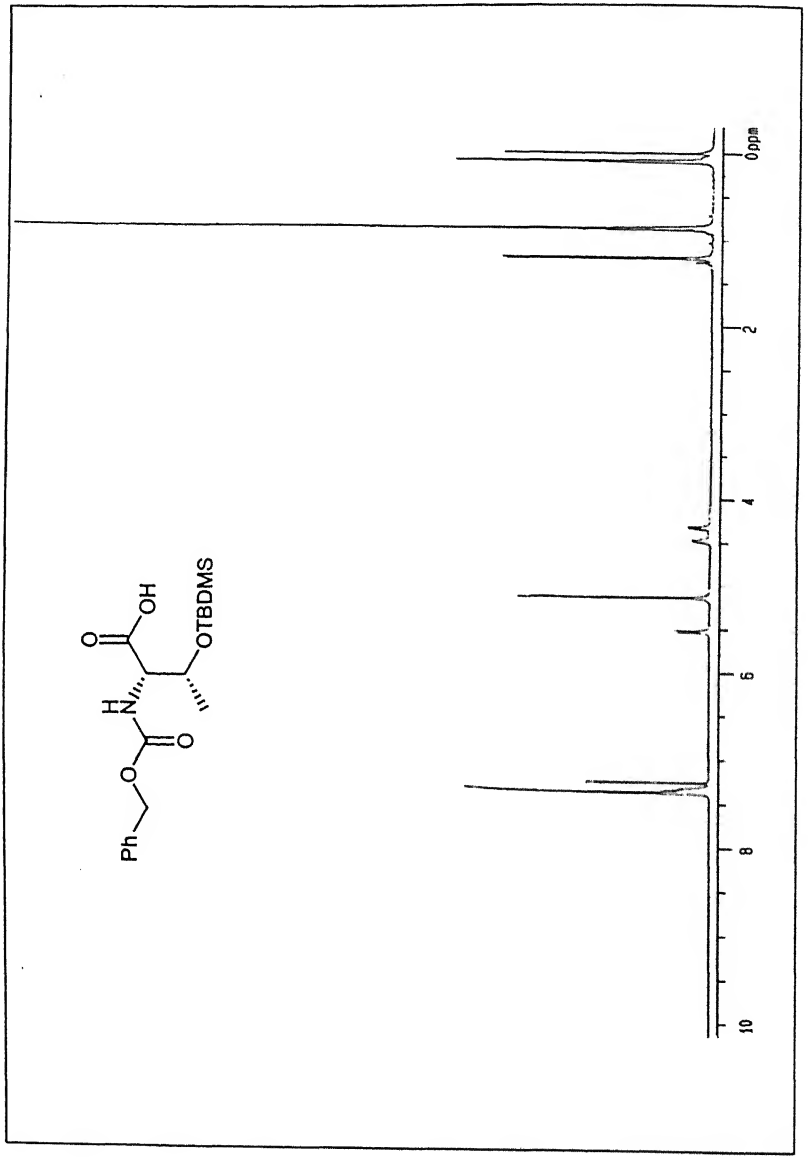


Figure 3.20 ^{1}H NMR spectrum of **201**

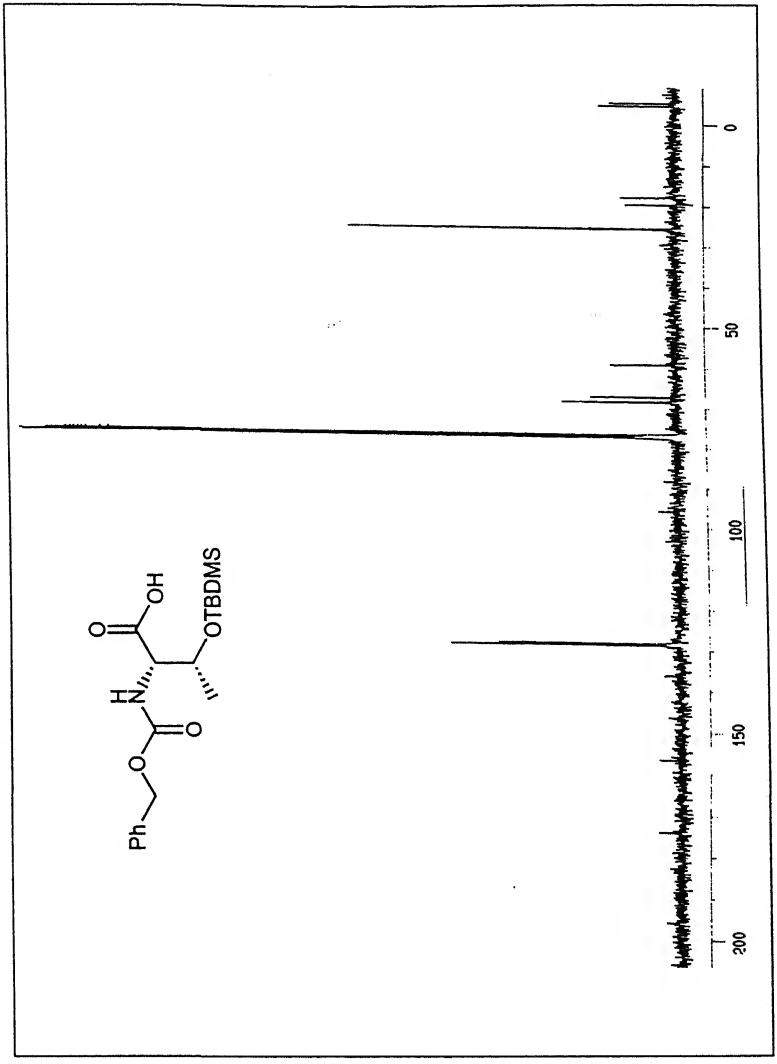


Figure 3.21 ^{13}C NMR spectrum of **201**

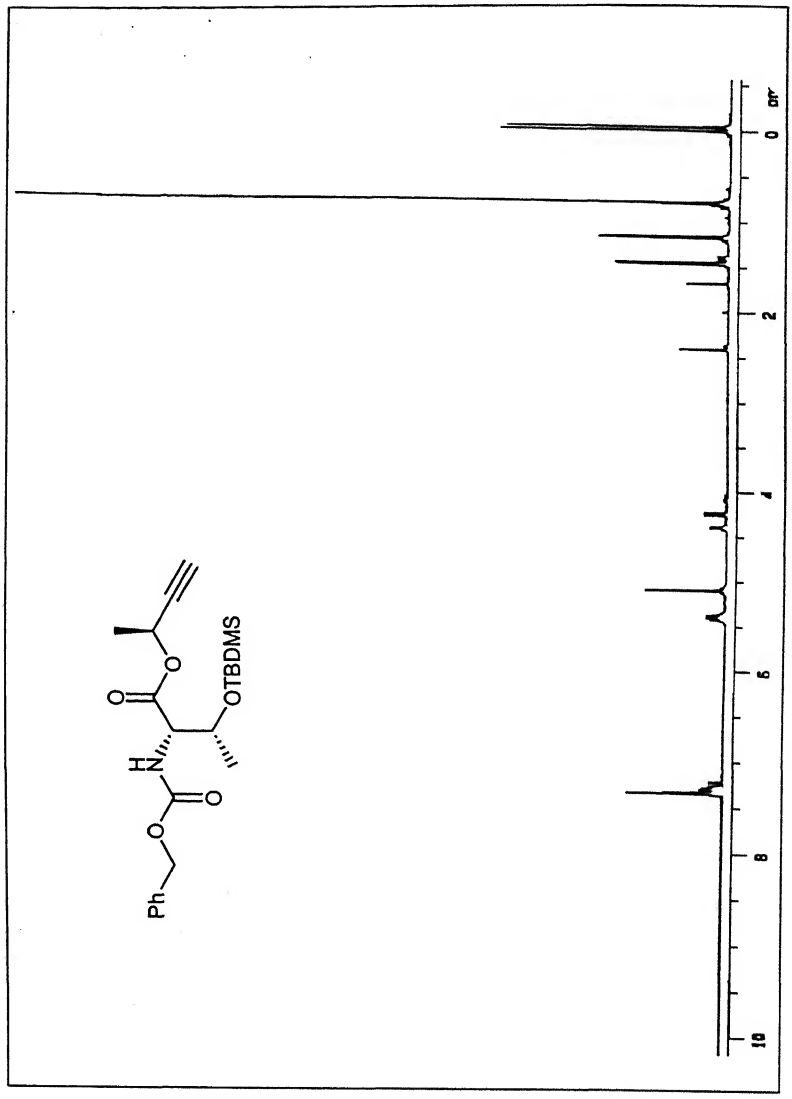


Figure 3.22 ^{1}H NMR spectrum of **202**

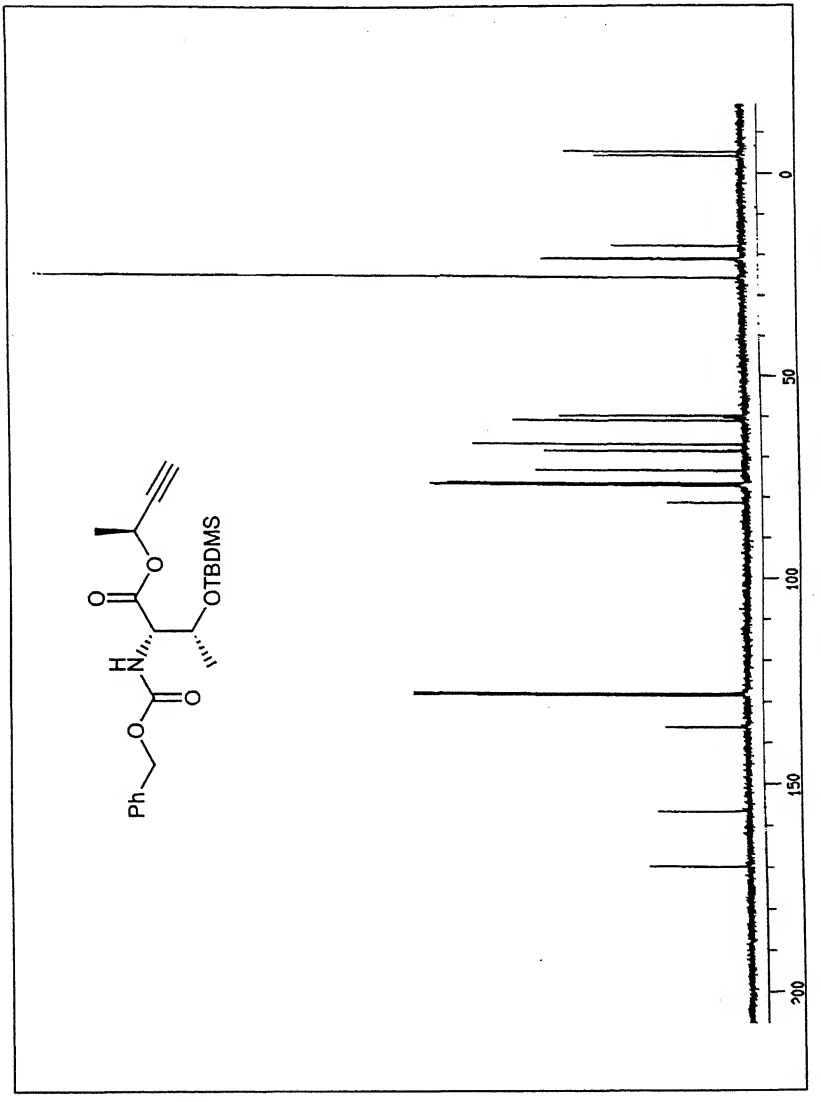


Figure 3.23 ^{13}C NMR spectrum of **202**

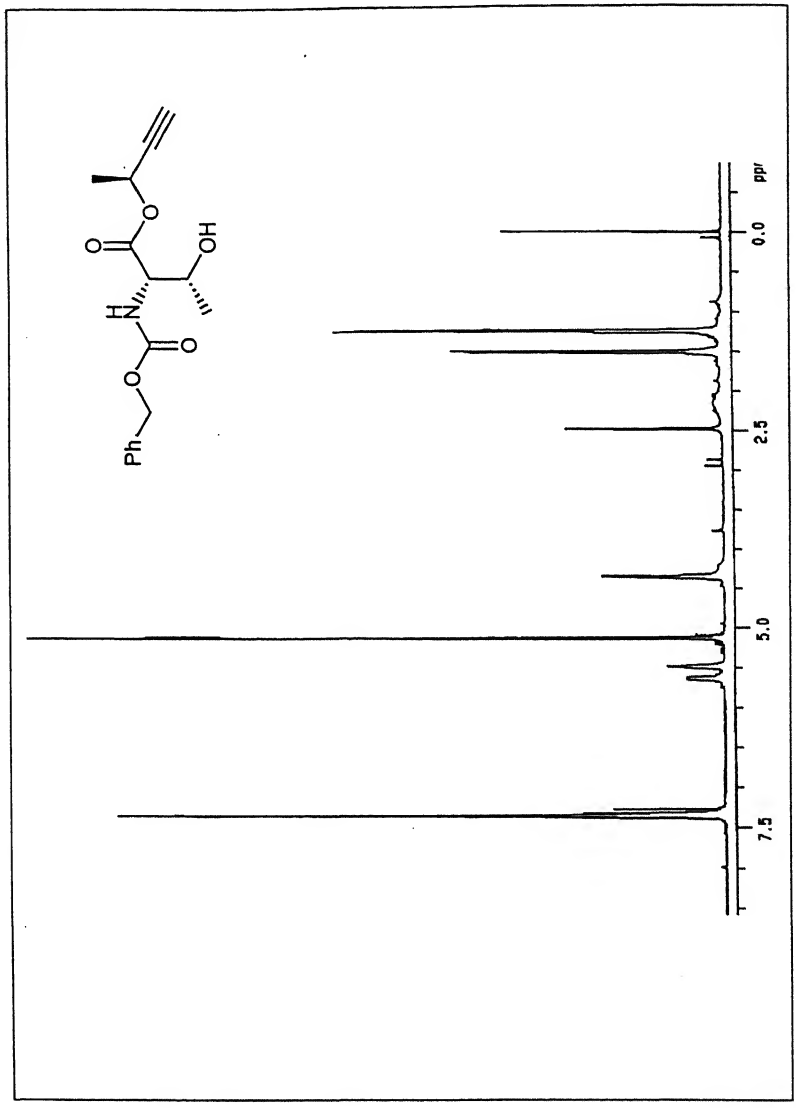


Figure 3.24 ^{1}H NMR spectrum of **203**

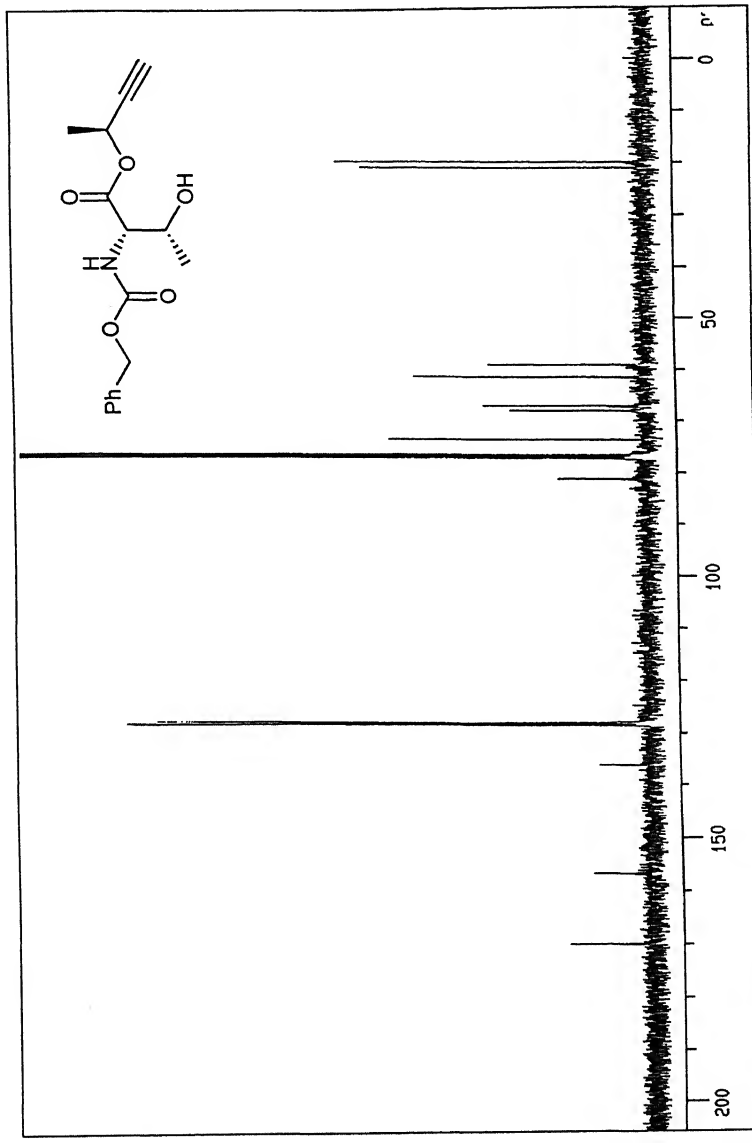


Figure 3.25 ^{13}C NMR spectrum of **203**

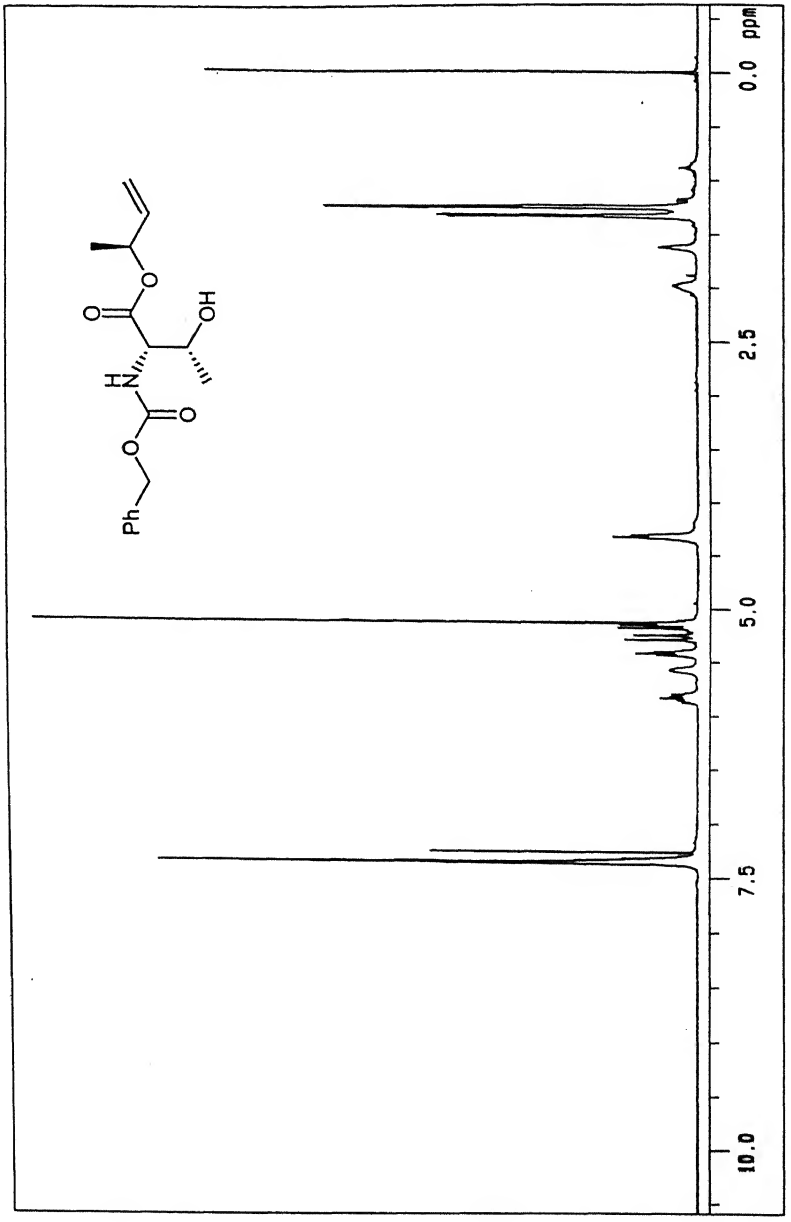


Figure 3.26 ^{1}H NMR spectrum of **204**

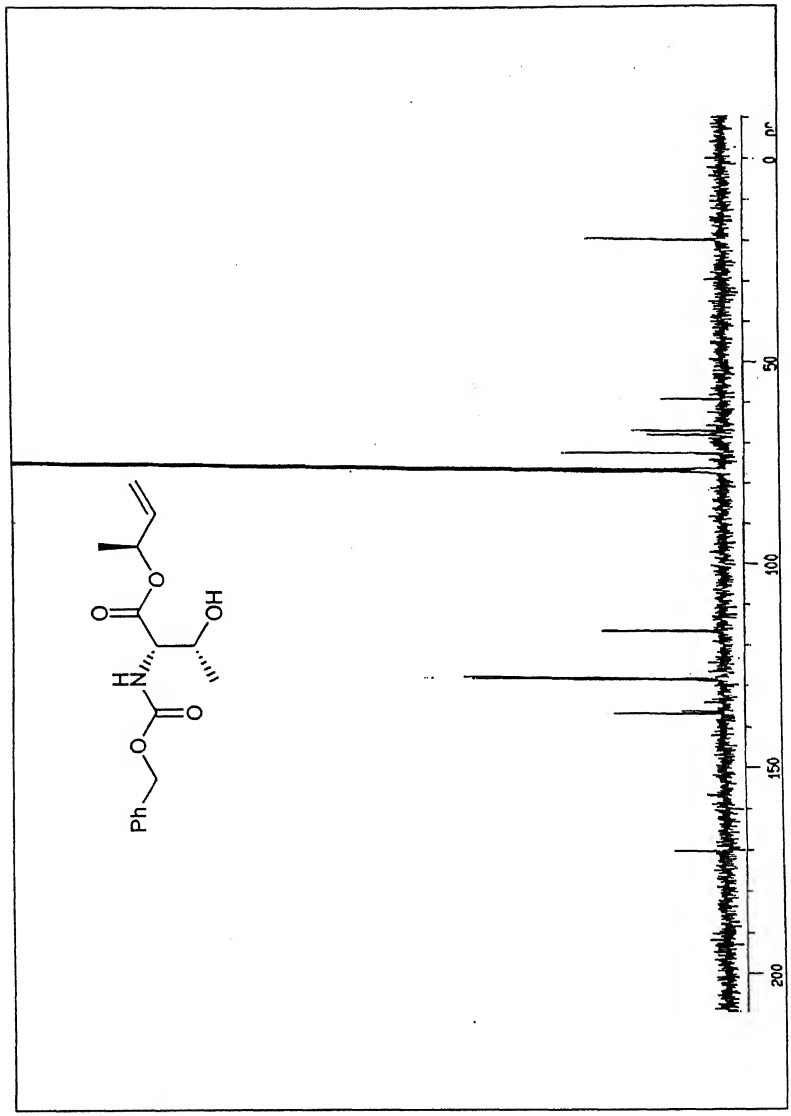


Figure 3.27 ^{13}C NMR spectrum of **204**

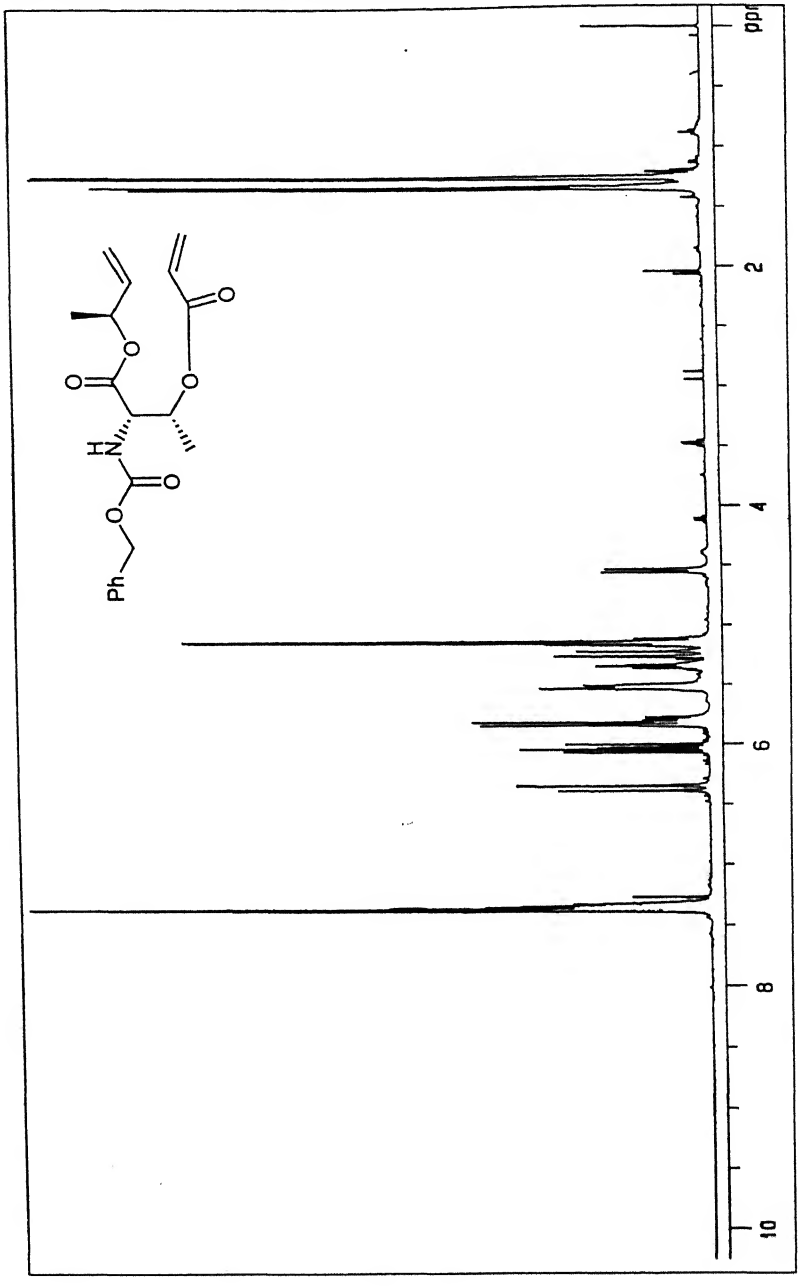


Figure 3.28 ^{1}H NMR spectrum of **198**

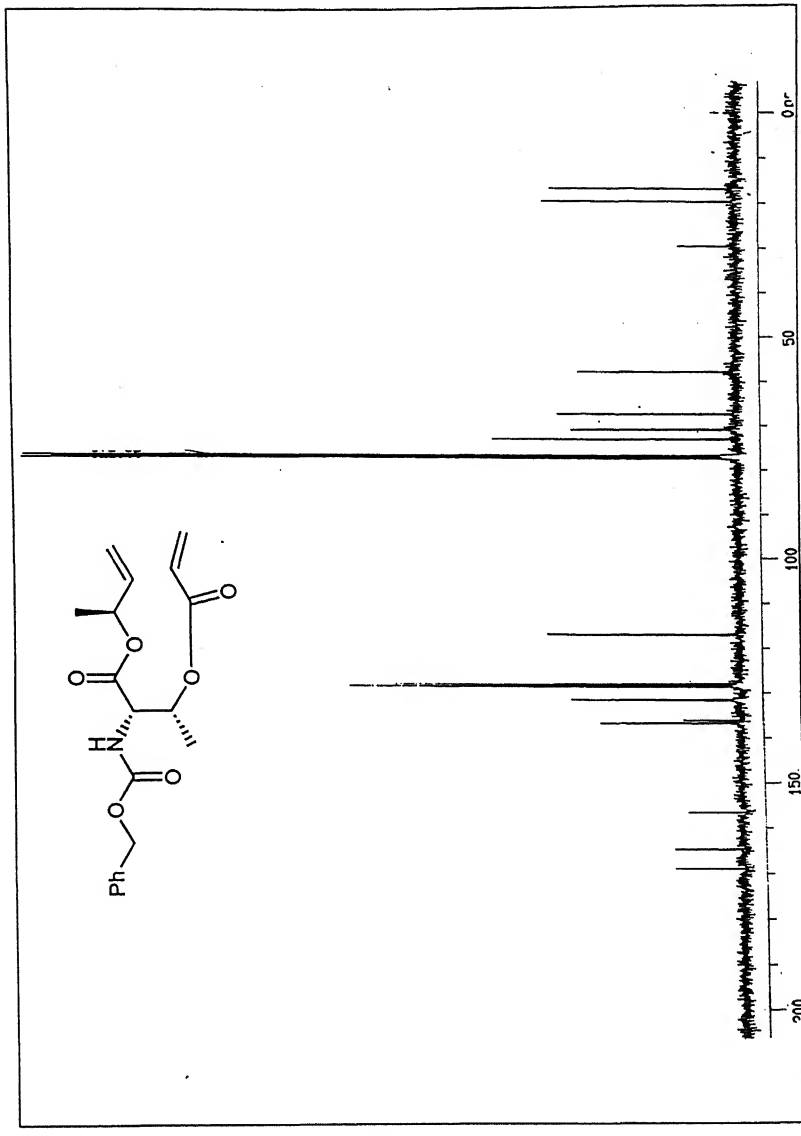


Figure 3.29 ^{13}C NMR spectrum of **198**

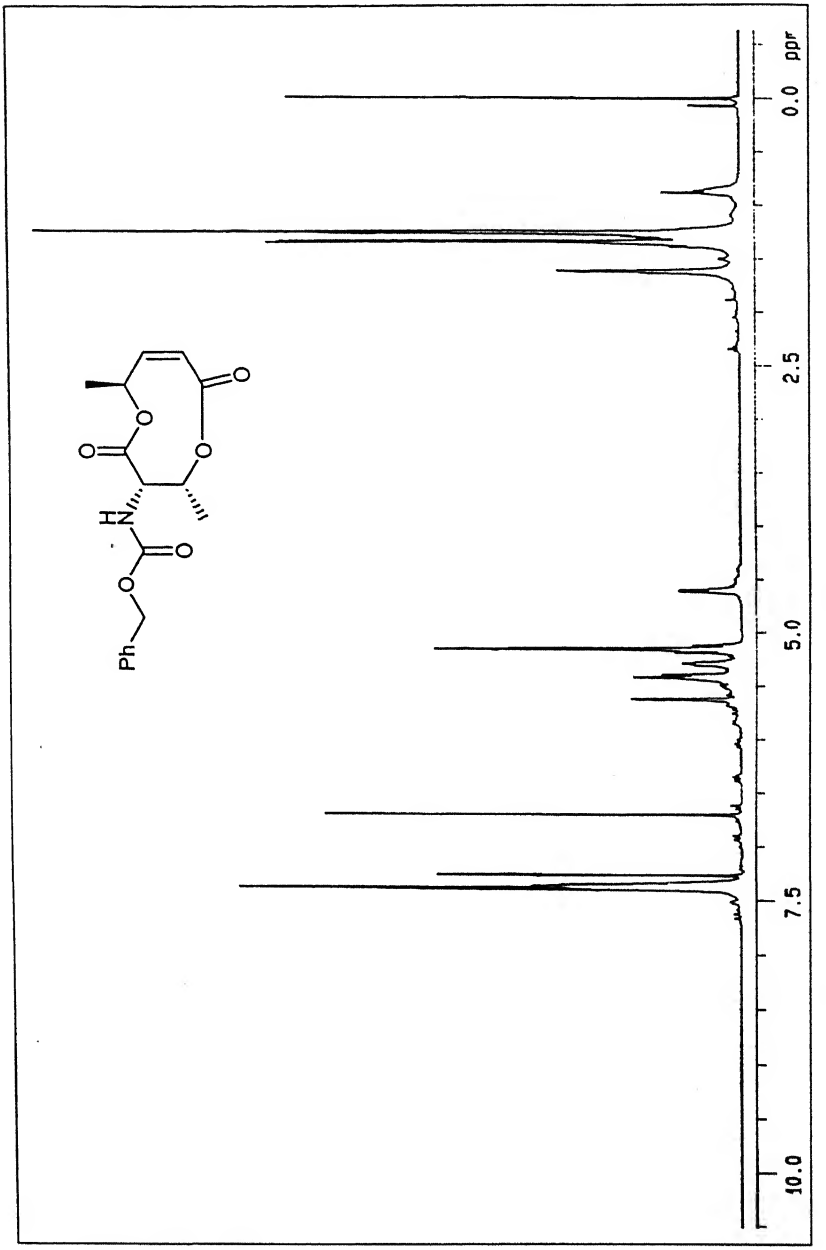


Figure 3.30 ^{1}H NMR spectrum of *cis*-**197**

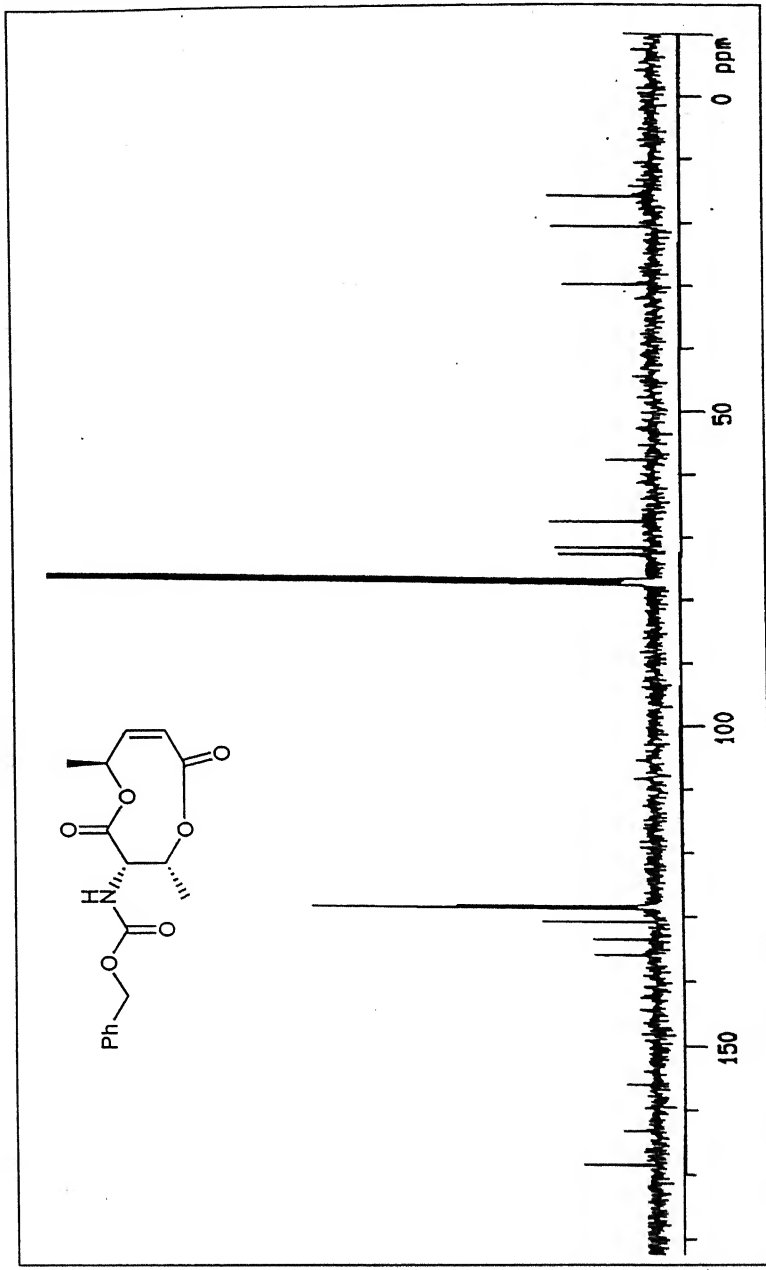


Figure 3.31 ^{13}C NMR spectrum of ***cis*-197**

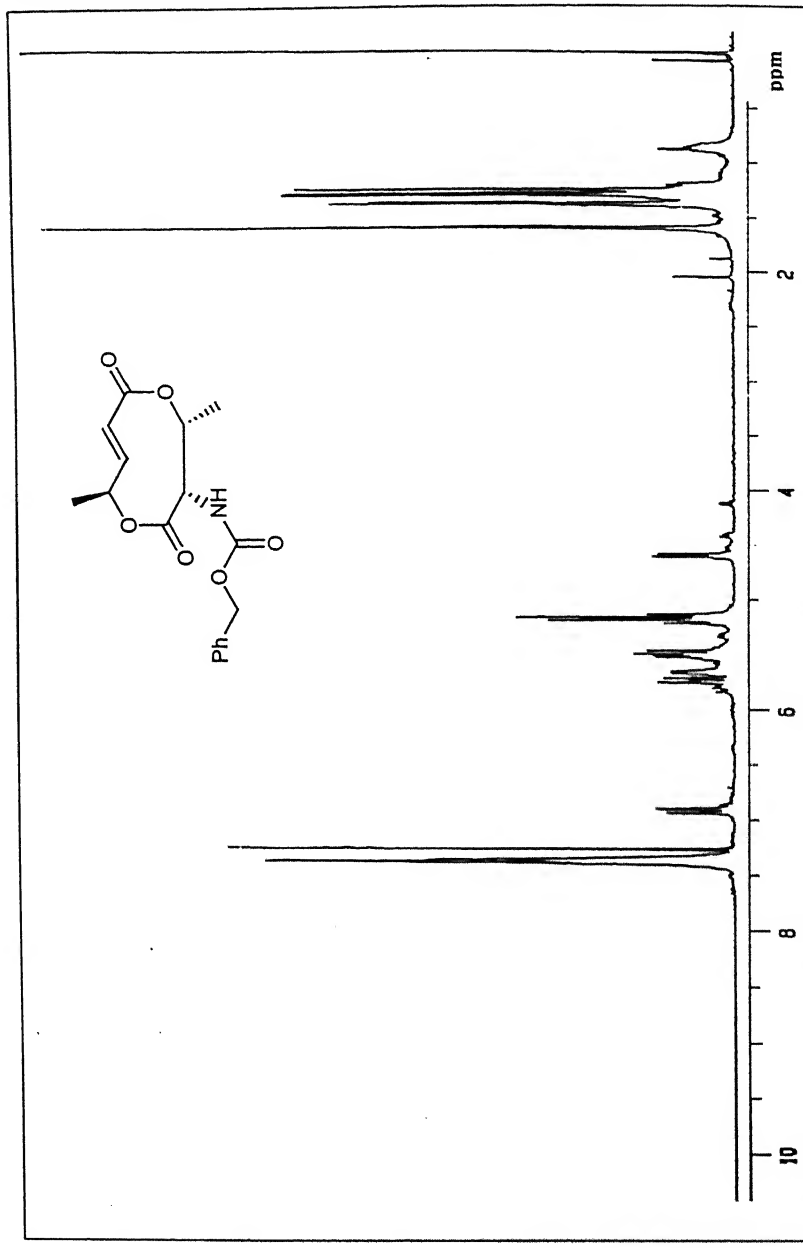


Figure 3.32 ^{1}H NMR spectrum of ***trans*-197**

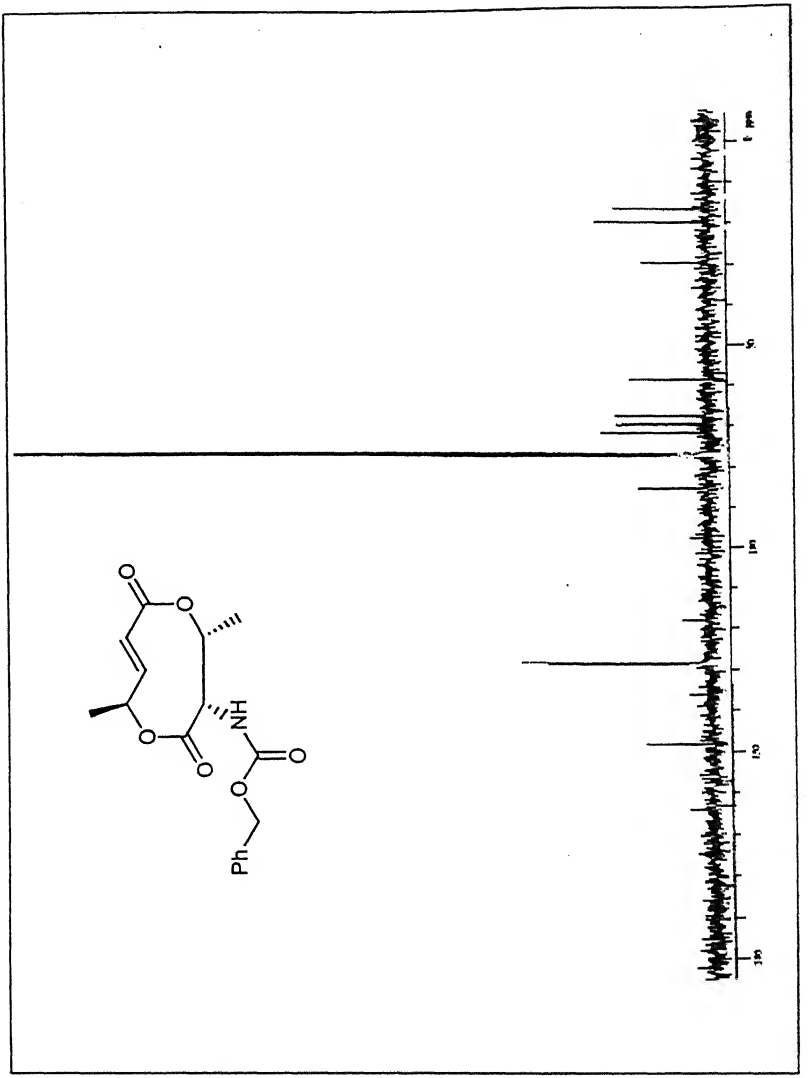


Figure 3.33 ^{13}C NMR spectrum of *trans*-197

References

1. Grubbs, R. H.; Pine, S. H. in *Comprehensive Organic Syntheis*, Trost, B. M.; Fleming, I.; Paquette, L. A. Eds.; Pergamon: New York, **1991**, *Vol. 5*, Chapter 9.3.
2. a) Caledron, N. *Acc. Chem. Res.* **1972**, *5*, 127. b) Caledron, N.; Chen, H. Y.; Scott, K, W. *Tetrahedron Lett.* **1967**, *8*, 3327. c) Caledron, N.; Ofstead, E. A.; Ward, J. P.; Judy, W. A.; Scott, K. W. *J. Am. Chem. Soc.* **1968**, *90*, 4133. d) Mol, J. C.; Moulijn, J. A.; Boelhouwer, C. *Chem. Commun.* **1968**, 633.
3. Grubbs, R.H.; Brunck, T.K. *J. Am. Chem. Soc.* **1972**, *94*, 2538.
4. Herrison, J. L.; Chauvin, Y. *Makromol. Chem.* **1970**, *141*, 161.
5. a) Buchmeiser, M. R. *Chem. Rev.* **2000**, *100*, 1565-1604. b) Roy, R.; Das, S. K. *Chem. Commun.* **2000**, 519-529. c) Wright, D. L. *Curr. Org. Chem.* **1999**, *3*, 211-240. d) Randall, M. L.; Snapper, M. L. *J. Mol. Catal. A* **1998**, 133, 1-16. e) Noels, A. F.; Demonceau, A. *J. Phys. Org. Chem.* **1998**, *11*, 602-609. f) Naota, T.; Takaya, H.; Murahashi, S. –I. *Chem. Rev.* **1998**, *98*, 2599-2660.
6. For reviews, see: a) Buchmeiser, M. R. *Chem. Rev.* **2000**, *100*, 1565-1604. b) Stelzer, F. *J. Macromol. Sci. Chem.* **1996**, *A33*(7), 941. c) Schrock, R. R. in *Ring-Opening Polymerization* (Ed.: D. J. Brunelle), Hanser, München, **1993**, p. 129-156. d) Grubbs, R. H.; Tumas, W. *Science* **1989**, *243*, 907-915.
7. Tsuji, J.; Hashiguchi, S. *Tetrahedron Lett.* **1980**, *21*, 2955.

8. For reviews, see: a) Grubbs, R. H.; Trnka, T. M. *Acc. Chem. Res.* **2001**, *34*, 18-29. b) Kotha. S.; Sreenivasachary, N. *Ind. J. Chem.* **2001**, *40B*, 763-780. c) Fürstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3012-43. d) Maier, M. E. *Angew. Chem., Int, Ed.* **2000**, *39*, 2073-77. e) Phillips, A. J.; Abell, A. D. *Aldrichimica Acta* **1999**, *32*, 75-89. f) Grubbs, G. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413-50. g) Armstrong, S. K. *J. Chem. Soc., Perkin Trans. 1* **1998**, 371-88. h) Pariya, C.; Jayaprakash, K. N.; Sarkar, A. *Coord. Chem. Rev.* **1998**, *168*, 1-48. i) Schuster, M.; Blechert, S. *Angew. Chem., Int. Ed.* **1997**, *36*, 2036-56. j) Grubbs, R. H.; Miller, S. J.; Fu, G. C. *Acc. Chem. Res.* **1995**, *28*, 446-552. k) Schmalz, H. –G. *Angew. Chem., Int. Ed.* **1995**, *34*, 1833-36.
9. A) Grubbs, R. H.; *J. Macromol. Sci. Chem.* **1994**, *A31*(11), 1829. B) Schrock, R. R. *Pure Appl. Chem.* **1994**, *66*, 1447.
10. Katz, T. J.; Sivavec, T. M. *J. Am. Chem. Soc.* **1985**, *107*, 737.
11. Wallace, K. C.; Liu, A. H.; Dewan, J. C.; Schrock, R. R. *J. Am. Chem. Soc.* **1988**, *110*, 4964.
12. a) Kress, J.; Aguero, A.; Osborn, J. A. *J. Mol. Catal.* **1986**, *36*, 1-12. b) Quignard, F.; Leconte, M.; Basset, J. –M. *J. Chem. Soc., Chem. Commun.* **1985**, 1816.
13. a) Bazen, G. C.; Oskam, J. H.; Cho, H. –N,; Park, L.Y.; Schrock, R. R. *J. Am. Chem. Soc.* **1991**, *113*, 6899. b) Schrock, R. R.; Feldman, J.; Cannizo, L. F.; Grubbs, R. H. *Macromolecules*, **1987**, *20*, 1169. c) For a review, see: Schrock, R. R. *Tetrahedron* **1999**, *55*, 8141.

14. Kirkland, T. A.; Grubbs, R. H. *J. Org. Chem.* **1997**, *62*, 7310.

15. Fürstner, A.; Langemann, K. *J. Org. Chem.* **1996**, *61*, 8746.

16. a) Fu, G. C.; Grubbs, R. H. *J. Am. Chem. Soc.* **1992**, *114*, 5426. b) Fu, G. C.; Grubbs, R. H. *J. Am. Chem. Soc.* **1992**, *114*, 7324.

17. Shon, Y. –S.; Lee, T. R. *Tetrahedron Lett.* **1997**, *38*, 1283.

18. Huwe, C. M.; Velder, J.; Blechert, S. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2376.

19. Kim. S. –H.; Zuercher, W. J.; Bowden, N. B.; Grubbs, R. H. *J. Org. Chem.* **1996**, *61*, 1073.

20. a) Nguyen, S. T.; Johnson, L. K.; Grubbs, R. H. *J. Am. Chem. Soc.* **1992**, *114*, 3974. b) Wu, Z.; Nguyen, S. T.; Grubbs. R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1995**, *117*, 5503. c) Fu, G. C.; Nguyen. S. T.; Grubbs, R. H. *J. Am. Chem. Soc.* **1993**, *115*, 9856.

21. Maier, M. E.; Langenbacher, D.; Rebein, F. *Liebigs Ann.* **1995**, 1843.

22. Fürstner, A.; Kindler, N. *Tetrahedron Lett.* **1996**, *37*, 7005.

23. Fujimura, O,; Fu, G. C.; Grubbs. R. H. *J. Org. Chem.* **1994**, *59*, 4029.

24. Armstrong, S. K.; Christie, B. A. *Tetrahedron Lett.* **1996**, *37*, 9373.

25. a) Schwab, P.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 100. b) Schwab, P.; France, M. B.; Ziller, J. W.; Grubbs, R. H. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2039.

26. Crimmins, M. T.; King, B. W. *J. Org. Chem.* **1996**, *61*, 4192.

27. Zuercher, W. J.; Hashimoto, M.; Grubbs, R. H. *J. Am. Chem. Soc.* **1996**, *118*, 6634.

28. Miller, S. J.; Blackwell, H. E.; Grubbs. R. H. *J. Am. Chem. Soc.* **1996**, *118*, 9606.

29. a) Bertinato, P.; Sorensen, E. J.; Meng, D.; Danishefsky, S.J. *J. Org. Chem*, **1996**, *61*, 8000. b) Meng, D.; Su, D, -S.; Balog, A.; Bertinato, P.; Sorensen, E. J.; Danishefsky, S. J.; Zheng, Y. –H.; Chou, T. –C.; He, L.; Horwitz, S.B. *J. Am. Chem. Soc.* **1997**, *119*, 2733.

30. a) Nicolaou, K. C.; He, Y.; Vourloumis, D.; Vallberg, H.; Yang, Z. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2399. b) Nicalaou, K. C.; Winssinger, N.; Pastor, J.; Ninkovic, S.; Sarabia, F.; He, Y.; Vourloumis, D.; Yang, Z.; Li, T.; Giannakakou, P.; Hamel, E. *Nature*, **1997**, *387*, 268.

31. Dias, E. L.; Nguyen, S.T.; Grubbs. R. H. *J. Am. Chem. Soc.* **1997**, *119*, 3887.

32. Cucullu, M. E.; Li, C.; Nolan, S. P.; Nguyen, S. T.; Grubbs, R. H. *Organometallics*, **1998**, *17*, 5565.

33. Weskamp, .; Schattenmann, W.C.; Spiegler, M.; Herrmann, W. A. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 2490.

34. Bourissou, D.; Guerret, O.; Gabbai, F. P.; Bertrand, G. *Chem. Rev.* **2000**, *100*, 39-91.

35. Scholl, M.; Trnka, T. M.; Morgan, J. P.; Grubbs, R. H. *Tetrahedron Lett.* **1999**, *40*, 2247.

36. Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953.

37. Chattejee, A. K.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 1751.

38. Kingsbury, J. S.; Harrity, P. A.; Bonitatebus, A. H.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1999**, *121*, 791.

39. Fürstner, A.; Hill, A. F.; Liebl, Eilton-Ely, J. D. E. T. *Chem. Commun.* **1999**, 601.

40. a) Weskamp, T.; Schattenmann, W. C.; Spiegler, M.; Herrmann, W. A. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 2490. b) Ackermann, L.; Fürstner, A.; Weskamp, T.; Kohl, F. J.; Herrmann, W. A. *Tetrahedron Lett.* **1999**, *40*, 4787.

41. Clercq, B. D.; Verpoort, F. *Tetrahedron Lett.* **2002**, *43*, 9101.

42. Rainier, J. D.; Cox, J. M.; Allwein, S. P. *Tetrahedron Lett.* **2001**, *42*, 179.

43. Okada, A.; Ohshima, T.; Shibasaki, M. *Tetrahedron Lett.* **2001**, *42*, 8023.

44. Maynard, H. D.; Grubbs, R. H. *Tetrahedron Lett.* **1999**, *40*, 4137.

45. Paquette, L.A.; Schloss, J.D.; Efremov, I.; Fabris, F.; Gallou, F.; Mèndez-Andino, J.; Yang, J. *Org. Lett.* **2000**, *2*, 1259.

46. Ahn, Y. M.; Yang, K. –L.; Georg, G. I. *Org. Lett.* **2001**, *3*, 1411.

47. Ahmed, M.; Barrett, A. G. M.; Braddock, D. C.; Cramp, S. M.; Procopiou, P.A. *Tetrahedron Lett.* **1999**, *40*, 8657.

48. Hansen, T. V. *Tetrahedron: Asymmetry.* **2002**, *13*, 547.

49. Ginesta, X,; Pericàs, M. A.; Riera. A. *Tetrahedron Lett.* **2002**, *43*,779.

50. Pachamuthu, K.; Vankar, Y. D. *J. Organomet. Chem.* **2001**, *624*, 359.

51. Buszek, K. R.; Sato, N.; Jeong, Y. *Tetrahedron Lett.* **2002**, *43*, 181.

52. Boiteau, J, -G.; Van de Weghe, P.; Eustache, J. *Org. Lett.* **2001**, *3*, 2737.

53. Cossy, J.; Wills, C.; Bellosta, V.; BouzBouz, S. *J. Org. Chem.* **2002**, *67*, 1982.

54. Crimmins, M. T.; Emmite, K. A.; Choy, A. L. *Tetrahedron* **2002**, *58*, 1817.

55. Sabat, M.; Johnson, C, R. *Tetrahedron Lett.* **2001**, *42*, 1209.

56. Hagiwara, H.; Katsumi, T.; Kamat, V. P.; Hoshi, T.; Suzuki, T.; Ando, M. *J. Org. Chem.* **2000**, *65*, 7231.

57. Fürstner, A.; Thiel, O. R.; Ackermann. *Org. Lett.* **2001**, *3*, 449.

58. Fürstner, A.; Radkowski, K. *Chem. Commun.* **2001**, 671.

59. For applications of **68** in total synthesis, see: (a) Fürstner, A.; Thiel, O. R. *J. Org. Chem.* **2000**, *65*, 1738. (b) Fürstner, A.; Grabowski, J.; Lehmann, C. W.; Kataoka, T.; Nagai, K. *ChemBioChem*, **2001**, *2*, 60.

60. For a recent example showing the dramatic influence of protecting groups on the stereochemical coarse of RCM, see: Fürstner, A.; Thiel, O. R.; Blanda. *Org. Lett*, **2000**, *2*, 3731.

61. a) Snider, B. B.; Song, F. *Org. Lett.* **2001**, *3*, 1817. b) Fürstner, A.; Seidel, G.; Kindler, N. *Tetrahedron* **1999**, *55*, 8215.

62. Murga, J.; Falomir, E.; Garcia-Fortanet, J.; Carda, M.; Marco, J. A. *Org. Lett.* **2002**, *4*, 3447.

63. Smith, A. B., III; Adams, C. M.; Kozmin, S. A. *J. Am. Chem. Soc.* **2001**, *123*, 990.

64. Baltrusch, A. W.; Bracher, F. *Synlett.* **2002**, 1724.

65. Banwell, M. G.; Jolliffe, K. A.; Loong, D. T. J.; McRae, K. J.; Vounatsos, F. *J. Chem. Soc., Perkin Trans. 1* **2002**, 22.

66. Dixon, D. J.; Foster, A. C.; Ley, S. V. *Org. Lett.* **2000**, *2*, 123.

67. a) For a reviews on enyne metathesis, see: Mori, M.; *Top. Organomet. Chem.* **1998**, *1*, 133. b) Mori, M.; Kitamura, T.; Sato, Y. *Synthesis* **2001**, 654. c) Kinoshita, A.; Sakakibara, N.; Mori, M. *Tetrahedron* **1999**, 8155.

68. a) Kinoshita, A.; Mori, M. *Heterocycles* **1997**, *46*, 287. b) Renaud, J.; Graf, C. –D.; Oberer, L. *Angew. Chem., Int. Ed.* **2000**, *39*, 3101. c) Barrett, A. G. M.; Baugh, S. P. D.; Braddock, D. C.; Flack, K.; Gibson, V. C.; Giles, M. R.; Marshall, E. L.; Procopiou, P. A.; White, A. J. P.; Williams, D. J. *J. Org. Chem*, **1998**, *63*, 7893. d) Kotha, S.; Sreenivasachary, N.; Brahmachary, E. *Eur. J. Org. Chem.* **2001**, *4*, 787.

69. a) Katz, T. J.; Sivavec, T. M. *J. Am. Chem. Soc.* **1985**, *109*, 737. b) Hoye, R. T.; Donaldoson, S. M.; Vos, T. *Org. Lett.* **1999**, *1*, 277.

70. Fürstner, A.; Dierkes, T.; Thiel, O, R.; Blanda, G. *Chem. Europ. J.* **2001**, *7*, 5286.

71. a) For recent reviews, see: Alali, F. Q.; Liu, X, -X.; McLaughlin, J. L. *J. Nat. Prod.* **1999**, *62*, 504. b) Rao, Y. S. *Chem. Rev.* **1976**, *76*, 625.

72. Rupprecht, J. K.; Hui, J. –H.; McLaughlin, J. L. *J. Nat. Prod.* **1990**, *53*, 237.

73. Ribbons, D. W.; Sutherland, A. G. *Tetrahedron* **1994**, *50*, 3587.

74. Schiehser, G. A.; White, J. D.; Matsumoto, G.; Pezzanole, J. O.; Clardy, J. *Tetrahedron Lett.* **1986**, *27*, 5587.

75. Miller, M.; Hegedus, L. S. *J. Org. Chem.* **1993**, *58*, 6779.

76. Trost, B. M.; Muller, T. J. *J. Am. Chem. Soc.* **1994**, *116*, 4985.

77. For reviews, see: a) Figadère, B. *Acc. Chem. Res.* **1995**, *28*, 359. b) Hoppe, R.; Scharf, H. –D, *Synthesis* **1995**, 1447.

78. Naganuma, S.; Sakai, K.; Hasumi, K.; Endo, A. *J. Antibiot.* **1992**, *45*, 1216.

79. a) De Vries, V. G.; Schaffer, S. A.; Largis, E. E.; Dutia, M. D.; Wang, C. –H.; Bloom, J. D.; Katocs, Jr., A. S. *J. Med. Chem*, **1986**, *29*, 1131. b) Tomoda, H.; Nishida, H.; Masuma, R.; Cao, J.; Okuda, S.; Omura, S. *J. Antibiot.* **1991**, *44*, 136-159.

80. Bell, F. P.: Arterial cholesterol esterification by acyl-CoA: cholesterol acyl transferase, its possible significance in atherogenesis and its inhibition by drugs. In *Pharmacological Control of Hyperlipidemia*; Prous, J. R. Ed.; Science Publishers: **1986**; pp. 409-422.

81. Heider, J. G.: Agents, which inhibit cholesterol esterification in the intestine and their potential value in the treatment of

hypercholesterolemia. In *Pharmacological Control of Hyperlipidemia*; Prous, J. R. Ed.; Science Publishers: **1986**; pp. 423-438.

82. a) Ishigami, K.; Kitahara, T. *Tetrahedron* **1995**, *51*, 6431. b) For biosynthesis of acaterin see: Sekiyama, Y.; Fujimoto, Y.; Hasumi, K.; Endo, A. *J. Org. Chem.* **2001**, *66*, 5649.
83. Seebach, D.; Züger, M. *Helv. Chim. Acta.* **1982**, *65*, 495.
84. Franck, X.; Figadère, B. *Tetrahedron Lett.* **2002**, *43*, 1449.
85. Tsuboi, S.; Sakamoto, J.; Kawano, T.; Utaka, M.; Takeda, A. *J. Org. Chem.* **1991**, *56*, 7177.
86. Gamard, P.; Sauriol, F.; Benhamou, N.; Bèlanger, R. R.; Paulitz, T. *J. Antibiot.* **1997**, *50*, 742.
87. Braun, M.; Rahematpura, J.; Bühne, C.; Paulitz, T. C. *Synlett* **2000**, 1070.
88. Raina, S.; Singh, V. K. *Tetrahedron* **1996**, *52*, 4479.
89. Chandrasekhar, M.; Raina, S.; Singh, V. K. *Tetrahedron Lett.* **2000**, *41*, 4969.
90. a) Chandrasekhar, M.; Chandra, K. L.; Singh, V. K. *Tetrahedron Lett.* **2002**, *43*, 2773. b) Chandrasekhar, M.; Chandra, K. L.; Singh, V. K. *ARKIVOC* **2002**, 34.
91. For reviews on Baylis-Hillman reaction, see: a) Basavaiah, D.; Rao, P. D.; Hyma, R. S. *Tetrahedron Lett.* **1996**, *52*, 8001. b) Ciganek, E. *Org. React.* **1997**, *51*, 201.

92. a) Aggarwal, V. K.; Emme, I.; Fulford, S. Y. *J. Org. Chem.* **2003**. ASAP article. b) Hine, J.; Chen, Y. –J. *J. Org. Chem.* **1987**, *52*, 2091.

93. a) Fürstner, A.; Dierkes, T. *Org. Lett.* **2000**, *2*, 2463. b) Nicolaou, K. C.; Rodriguez, R. M.; Mitchel, H. J.; van Delft, F. L. *Angew. Chem., Int. Ed.* **1998**, *37*, 1874.

94. a) Ghosh, A. K.; Liu, C. *Chem. Commun.* **1999**, 1743. b) Fürstner, A.; Langemann, K. *J. Am. Chem. Soc.* **1997**, *119*, 9130.

95. Anand, R. V.; Baktharaman, S.; Singh, V. K. *Tetrahedron Lett.* **2002**, *43*, 5393.

96. Vogel A. I. *Text Book of Practical Organic Chemistry*, 5th ed.; ELBS/Longman, 1989, p 592.

97. Xiao, X.; Bai, D.*SynLett.* **2001**, 535.

98. Ishida, T.; Wada, K. *J. C. S. Chem. Commun.* **1975**, 209.

99. Ishida, T.; Wada, K. *J. C. S. Chem. Commun.* **1976**, 340.

100. Moore, B. P.; Brown, W. V. *Aust. J. Chem.* **1976**, *29*, 1365.

101. Ishida, T.; Wada, K. *J. C. S. Perkin Trans 1* **1979**, 323.

102. Tsuji, J.; Mandai, T. *Tetrahedron Lett.* **1978**, 1817.

103. Ireland, R. E.; Brown, Jr., F. R. *J. Org. Chem.* **1980**, *45*, 1868.

104. Wakamatsu, T.; Akasaka, K.; Ban, Y. *J. Org. Chem.* **1979**, *44*, 2008.

105. Boeckman, Jr., R. K.; Pruitt, J. R. *J. Am. Chem. Soc.* **1989**, *111*, 8286.

106. For isolation of antimycin A_3, see: Lockwood, J. L.; Leben, C.; Keitt, G. W. *Phytopathology* **1954**, *44*, 438. b) For structural

determination, See: Kinoshita, M.; Aburaki, S.; Umezawa, S. *J. Antibiot.* **1972**, *25*, 373.

107. Liu, W, -C.; Strong, F. M. *J. Am. Chem. Soc.* **1959**, *81*, 4387.

108. a) Miyoshi, H.; Tokutake, N.; Imaeda, Y.; Akagi, T.; Iwamura, H. *Biochim. Biophys. Acta* **1995**, *1229*, 149. b) Kim, H.; Essar, L.; Hossain, M. B.; Xia, D.; Yu, C. A.; Rizo, J.; Van der Helm, D.; Deisenhofer, J. *J. Am. Chem. Soc.* **1999**, *121*, 4902, and references cited therein.

109. a) Kinoshita, M.; Wada, M.; Aburagi, S.; Umezawa, S. *J. Antibiot.* **1971**, *24*, 724. b) Kinoshita, M.; Aburaki, S.; Wada, M.; Umezawa, S. *Bull. Chem. Soc. Jpn.* **1973**, *46*, 1279. c) Aburaki, S.; Kinoshita, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 198.

110. Corey, E. J.; Nicolaou, K. C. *J. Am. Chem. Soc.* **1974**, *96*, 5614.

111. Kinoshita, M.; Umezawa, S. *Bull. Chem. Soc. Jpn.* **1969**, *42*, 854.

112. a) Wasserman, H. H.; Gambale, R. J. *J. Am. Chem. Soc.* **1985**, *107*, 1423. b) Wasserman, H. H.; Gambale, R. J. *Tetrahedron* **1992**, *48*, 7059.

113. Inghardt, T.; Frejd, T. *Tetrahedron* **1991**, *47*, 6483.

114. a) Nakata, T.; Fukui, M.; Oishi, T. *Tetrahedron Lett.* **1983**, *24*, 2657. b) Tsunoda, T.; Nishii, T.; Yoshizuka, M.; Yamasaki, C.; Suzuki, T.; Itô, S. *Tetrahedron Lett.* **2000**, *41*, 7667.

115. a) Mulzer, J. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 6, pp. 323-380. b) Nicoloau, K.C. *Tetrahedron* **1977**, *33*, 683. c) Masamune, S.;

Bates, G. S.; Corcoran, W. *Angew. Chem., Int. Ed.* **1977**, *16*, 585. d) Back, T. G. *Tetrahedron* **1977**, *33*, 3041.

116. a) *Macrolides*; Omura, S., Ed.; Academic Press: New York, 1984. b) Boeckman, R. K., Jr.; Goldstein, S. W. *Total Synth. Nat. Prod.* **1988**, *7*, 1.

117. a) Shiina, I.; Kubota, M.; Ibuka, R. *Tetrahedron Lett.* **2002**, *43*, 7535. b) Keck, G. E.; Sanchez, C.; Wager, C. A. *Tetrahedron Lett.* **2000**, *41*, 8673. c) Ookoshi, T.; Onaka, M. *Tetrahedron Lett.* **1998**, *39*, 293. d) Ishihara, K.; Kubota, M.; Kurihara, H.; Yamamoto, H. *J. Org. Chem.* **1996**, *61*, 4560. e) Corey, E. J.; Nicolaou, K. C. *J. Am. Chem. Soc.* **1974**, *96*, 5614. f) Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989. g) Mukaiyama, T.; Usui, M.; Saigo, K. *Chem. Lett.* **1976**, 49.

118. For total synthesis of (*R*)-phoracantholide, see: a) Posner, G. H.; Wang, Q.; Halford, B. A.; Elias, J. S.; Maxwell, J. P. *Tetrahedron Lett.* **2000**, *41*, 9655. b) Sharma, A.; Chattopadhyay, S. *Molecules*, **1998**, *3*, 44. c) Jones, G. B.; Huber, R. S.; Chapman, B. J. *Tetrahedron: Asymmetry* **1997**, *8*, 1797. d) Saikia, A. K.; Hazarika, M. J.; Barua, N. C.; Bezbarua, M. S.; Sharma, R. P.; Ghosh, A. C. *Synthesis*, **1996**, 981. e) Ballini, R.; Marcantoni, E.; Petrini, M. *Liebigs Ann.* **1995**, 1381. f) Enders, D.; Plant, A.; Drechel, K.; Prokopenko, O. F. *Liebigs Ann.* **1995**, 1127. g) Nagumo, S.; Suemune, H.; Sakai, K. *Tetrahedron* **1992**, *48*, 8667, and references therein.

119. Hatch, R. P.; Shringarpure, J.; Weinreb, S. M. *J. Org. Chem.* **1978**, *43*, 4172.

120. Similar problems with RCM reactions of dienes containing thioether functions have been reported in the literature. For references, see: a) Fürstner, A.; Siedel, G.; Kindler, N. *Tetrahedron* **1999**, *55*, 8215. b) Shon, Y. –S.; Lee, T. R. *Tetrahedron Lett.* **1997**, *38*, 1283. c) Armstrong, S. K.; Christie, B. A. *Tetrahedron Lett.* **1996**, *37*, 9373. d) Mascarenas, J. L.; Rumbo, A.; Castedo, L. *J. Org. Chem.* **1997**, *62*, 8620.

121. For cleavage of methyl esters with BF_3OEt_2, see: Pearlman, B. A.; McNamara, J.M.; Hasan, I.; Hatakeyama, S.; Sekizaki, H.; Kishi, Y. *J. Am. Chem. Soc.* **1981**, *103*, 4248.

122. a) Ho, T. –L.; Ho, H. C.; Wong, C. M. *J. Chem. Soc., Chem. Commun.* **1971**, 750. b) Huurdemann, W. F. J.; Wynberg, H.; Emerson, D. W. *Tetrahedron Lett.* **1971**, *12*, 3449. c) Carins, J.; Logan, R. T. *J. C. S. Chem. Comm.* **1980**, 886. d) Komatsu, N.; Taniguchi, A.; Uda, M.; Suzuki, H. *Chem. Commun.* **1996**, 1847. e) Corey, E. J.; Erickson, B. W. *J. Org. Chem.* **1971**, *36*, 3553. f) Meshram, H. M.; Reddy, G. S.; Yadav, J. S. *Tetrahedron Lett.* , **1997**, *38*, 8891. g) Fujita, E.; Nagoa, Y.; Kaneko, K. *Chem. Pharm. Bull.* **1978**, *26*, 3743. h) Stork. G.; Zhao, K. *Tetrahedron Lett.* **1989**, *30*, 287.

123. Addition of highly oxophilic $Ti(OiPr)_4$ reduces the coordinating ability of the carbonyl group towards Ru center and thereby reduces the deactivation of the Ru carbene. See: reference 94.

124. Bodanzky, M.; Bodanzky, A. In *The Practice of Peptide Synthesis*. 2nd ed: Springer-Verlag, Berlin, 1994, p 48.

PART B

Development of Methodologies Under Solvent Free and Triphasic Conditions

Chapter 1

Thioacetalization of Carbonyl Compounds and Aziridine Ring Opening with Aromatic Amines under Solvent Free Conditions

1.1 Introduction

Sustainability is an increasingly important issue in the wider context dealing with population, health, the environment, renewable resources and in the sciences, as an integral part of the rapidly emerging field called Green Chemistry.[1] This is a multidisciplinary field, requiring integrated study in the chemical, biological and physical sciences as well as many aspects of engineering. The twelve principles of Green Chemistry, as defined by Anastas and Warner,[1] and generally accepted internationally, cover complex issues including waste minimization, reduction in energy usage and the use of renewable resources rather than depleting natural resources such as oil, coal, and gas.

Removing organic solvents in chemical synthesis is important in the drive towards benign chemical technologies. Organic solvents are high on the list of toxic or otherwise damaging compounds because of the large volumes used in industry, and difficulties in containing volatile compounds. Alternative reaction media include ionic liquids[2] (which have extremely low vapor pressure and can be recycled), liquid and supercritical CO_2,[3] water[4] (often at high temperature under microwave irradiation)[5] and polyethylene and polypropylene glycol[6]

(Figure 1). Another alternative is not to use a reaction medium, the so called "Solvent Free Reactions".[7,8] The choice of solventless or specific non-organic solvent reaction medium will depend on several issues including selectivity, yield, waste, ease of recycling and ease of isolation of products.

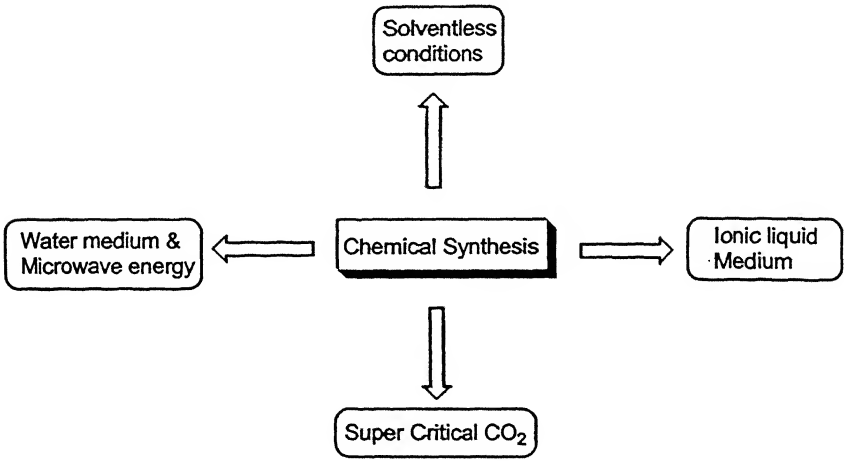


Figure 1.1

In using a reaction medium, there are many choices within each system, for example using ionic liquids with the appropriate hydrophobic-hydrophilic balance, and varying the density of liquid and supercritical CO_2, which can affect the stereo-chemical outcome of addition reactions.[3]

Advantages of using solventless reactions, relative to using organic or other reaction media include: (i) there is no reaction medium to collect, purify and recycle, (ii) the products formed are often sufficiently pure to circumvent extensive purification using chromatography, (iii) sequential solventless reactions are possible in

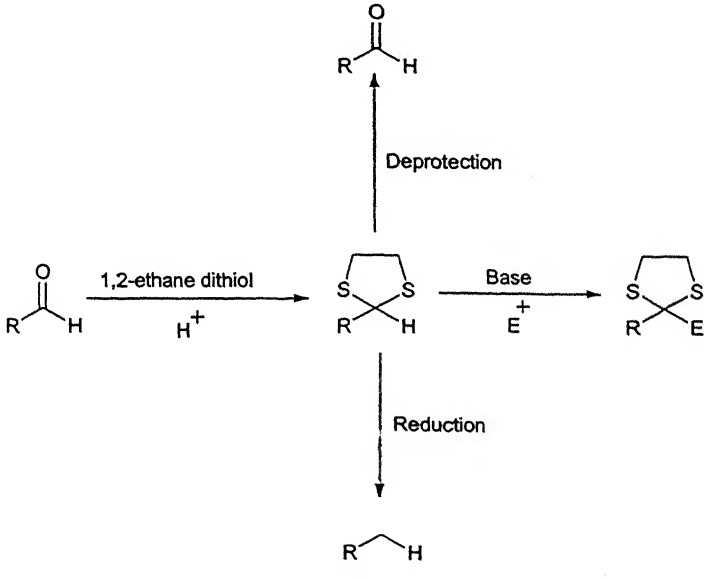
high yielding systems, (iv) atom economy[1d] and (iv) considerable batch size reduction and processing cost savings are achievable such that such solvent free protocols are not only more environmentally benign but are more economically feasible. These factors are especially important in industry.

Recently, supported reagents and catalysts on mineral oxide surfaces have been widely employed for solvent free organic synthesis.[9] Reagents immobilized on porous solid materials present a lot of advantages over the conventional solution phase reactions because of the good dispersion of active sites leading to improved reactivity and milder reaction conditions. Silica gel, alumina and Montmorillonite (K10) are the common supports used for this purpose. Solvent free reactions with supported reagents in combination with microwave (MW) irradiation, under so-called 'dry media' conditions, provides ideal reaction medium with special attributes such as reduced reaction times, easier work-up procedures as well as increased purity of products.[10]

Keeping in view our general interest in the development of environmentally friendly synthetic alternatives, we became interested in solvent free reactions. In this chapter, we wish to describe our efforts toward development of methodologies, like thioacetalization of carbonyl compounds and aziridine opening with aromatic amines, under solvent free conditions.

1.1.1 Thioacetalization of carbonyl compounds:

Thioacetalization of carbonyl compounds is an important transformation in organic synthesis.[11] Since the introduction of 1,3-dithianes as nucleophilic acylating reagents by Corey and Seebach, dithioacetals have become widely used tool for the formation of C–C bonds.[12] In addition, the stability exhibited by 1,3- and 1,2- dithiolanes under acidic and basic conditions has led to their synthetic utility as carbonyl protecting groups[11] and as intermediates in the conversion of a carbonyl function to either hydrocarbon derivatives[13] or to higher order carbonyl compounds (*Umpolung* synthesis) (Scheme 1.1).[14]

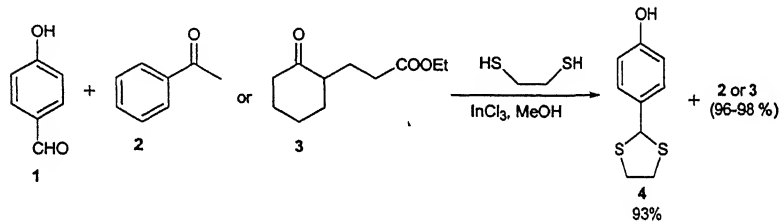


Scheme 1.1

Since thioacetalization is a protic or Lewis acid catalyzed transformation, a number of acid catalysts such as Zn or $Mg(OTf)_2$,[15] BF_3OEt_2,[16] $AlCl_3$,[17] $TiCl_4$,[18] $LaCl_3$,[19] etc. have been reported for this

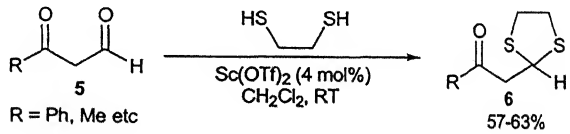
conversion. Numerous other methods that are reported for this transformation include the use of LiBr,[20] ceric amminium nitrate (CAN)[21] and $LiBF_4$.[22]

Recently, Muthusamy and co-workers reported a chemoselective thioacetalization of carbonyl compounds using $InCl_3$ as a catalyst.[23] When an equimolar mixture of *p*-hydroxy benzaldehyde (1) and acetophenone **2** or ketoester **3** was allowed to react with 1 equivalent of 1,2-ethanedithiol in the presence of catalytic amount of $InCl_3$, a high yield of **4** was obtained along with recovered **2** or **3** (Scheme 1.2).



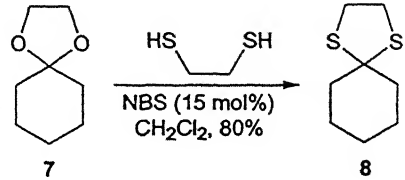
Scheme 1.2

Very recently, Kamal and co-workers used $Sc(OTf)_3$ as a recyclable Lewis acid catalyst for thioacetalization reactions.[24] This method has also been extended for the intramolecular chemoselectivity between keto and aldehyde functionalities (Scheme 1.3). Moreover, this catalyst has been recovered almost quantitatively from the aqueous layer and has been reused several times without losing its activity.



Scheme 1.3

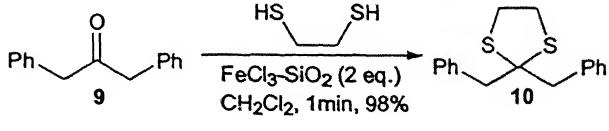
Kamal and co-workers have also found an efficient method for transthioacetalization[25] of acetals using NBS as a catalyst.[26] For example, treatment of **7** with 1,2-ethanedithiol in the presence of 15 mol% of NBS gave a thioacetal **8** in 80% yield under mild reaction conditions (Scheme 1.4).



7 **8**

Scheme 1.4

Solid acid catalysts[27] like HY zeolite[28] and Kaolinitic clay[29] have been reported in the literature for thioacetalization reactions. A number of solid supported reagents and Lewis acid catalysts have been developed to achieve this transformation. For example, *anhydrous* $FeCl_3$ dispersed on SiO_2 was found to be very efficient for the conversion of 1,3-diphenyl-2-propanone **9** to its corresponding thioacetal **10** in 98% yield within a minute (Scheme 1.5).[30]



9 **10**

Scheme 1.5

The other solid supported reagents such as $TaCl_5$-SiO_2,[31] $ZrCl_4$-SiO_2[32] and $CoBr_2$-SiO_2[33] have also been found to be efficient for thioacetalization reaction. The main reason for using supported reagents is due to their higher selectivity, milder reaction conditions and simple work-up procedures.

1.1.2 Aziridine Ring Opening with Amines:

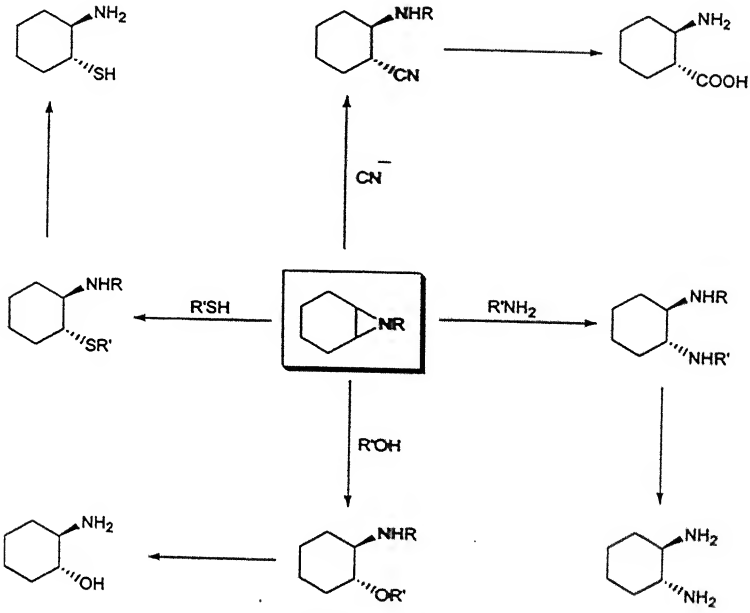
Aziridines are saturated three-membered heterocycles conaining one nitrogen atom. Since the mid 1960s, aziridines have been classified as 'activated' or 'nonactivated' according to whether or not nucleophilic ring-opening reactions proceed in the absence of positive charge at nitrogen[34] and this classification is intimately related to the nature of the substituent on the nitrogen atom of the heterocycle. The term 'activated aziridine' **11** (Figure 1.2) is suggested for those derivatives which contain a substituent capable of stabilizing a negative charge which is formed on the aziridine nitrogen in the transition state when the aziridine reacts with a nucleophile. The 'nonactivated aziridine' **12** (Figure 1.2) contains no such substituent on the nitrogen or aziridine's N atom is basic.

Figure 1.2

The combination of Baeyer strain inherent in the three-membered heterocycle and the electronegativity of the heteroatom induce aziridine to undergo ring cleavage reactions with nucleophiles.[35] Some of the important features of aziridine ring opening with various nucleophiles are schematically represented in Scheme 1.6.

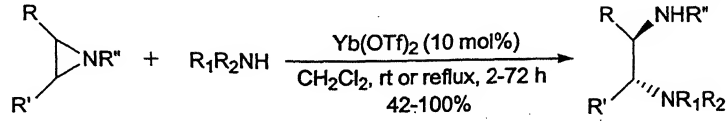
Nucleophilic ring opening of aziridines by amines is one of the simplest methods for the synthesis of *trans*-vicinal diamines. However,

this classical method has been disregarded primarily due to the limitations of the reaction conditions. The low nucleophilicity of amines required elevated temperature or vigorous reaction conditions.[36] However, this limitation can be eliminated by the use of Lewis acid catalysts.



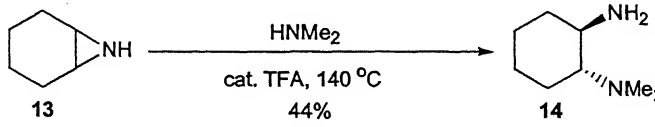
Scheme 1.6

Yamamoto and co-workers reported the first example of Lewis acid catalysed aminolysis of activated aziridines under mild conditions.[37] When 10-20 mol% of $Yb(OTf)_3$ was used as a catalyst, the aziridine cleavage proceeded very smoothly and yielded good to excellent amount of vicinal diamines (Scheme 1.7). It was found that in the absence of $Yb(OTf)_3$, the reaction was very slow and 20 % yield of the product was obtained after one week.



Scheme 1.7

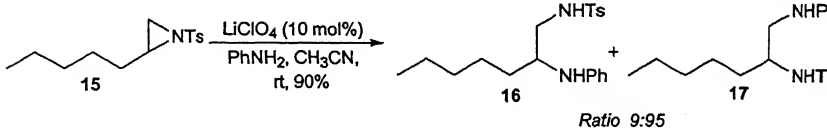
Very recently, trifluoroacetic acid catalysed ring opening of aziridine **13** with dimethyl amine has been reported.[38] The diamine **14** was obtained in 44% yield under very harsh conditions (Scheme 1.8).



13 14

Scheme 1.8

Yadav and co-workers have found that $LiClO_4$ efficiently catalyzes the ring opening of aziridines with a variety of aromatic amines.[39] For example, treatment of the *N*-tosyl aziridine **15** with aniline in the presence of 10 mol% of $LiClO_4$ gave a mixture of products **16** and **17** in 90% yield (Scheme 1.9). Aliphatic amines failed to react with aziridines even after a long reaction time at ambient temperature. The same group has also reported the $InBr_3$ catalysed highly efficient regioselective ring opening of aziridines with pyrrole.[40]



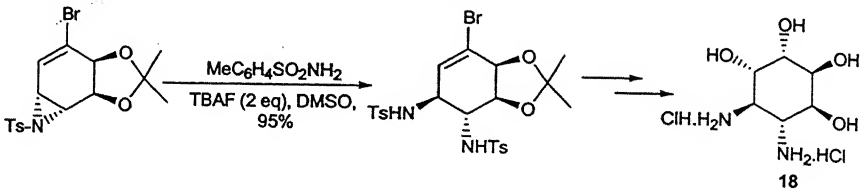
15 16 17

Ratio 9:95

Scheme 1.9

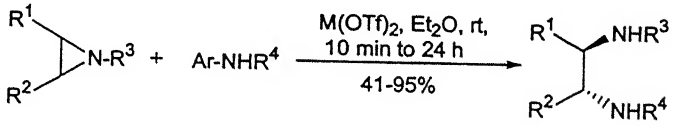
Recently, Hudlicky and co-workers have reported the synthesis of 3,4-diamino-3,4-dideoxy-*L-chiro*-inositol **18** through ring opening of

aziridines with *p*-toluene sulfonamide in the presence of tetrabutyl ammonium fluoride (TBAF) (Scheme 1.10).[41]



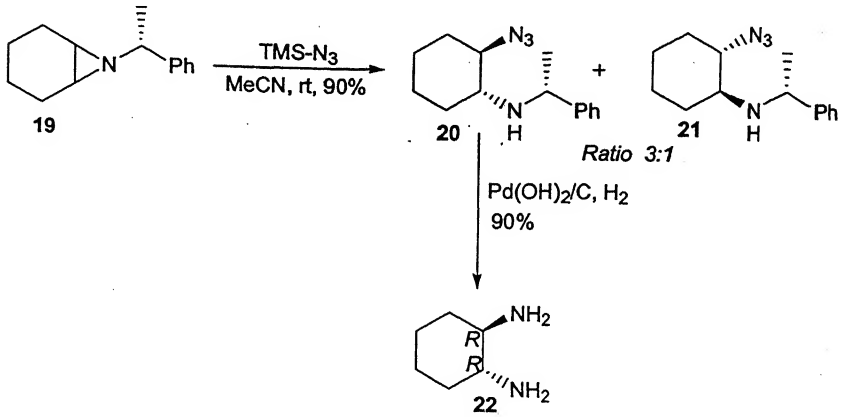
Scheme 1.10

We have reported that cyclic and acyclic vicinal diamines could be synthesized by ring opening of aziridines with aromatic amines in the presence of catalytic amounts of $Cu(OTf)_2$ or $Sn(OTf)_2$ (Scheme 1.11).[42] Although, the yield of products in the case of aromatic amines was excellent, aliphatic amine failed to react with aziridines.



Scheme 1.11

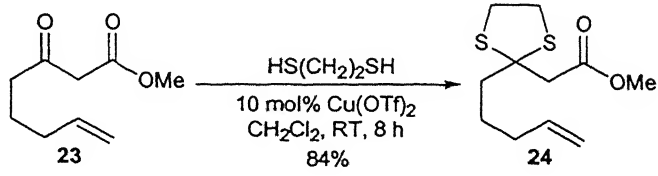
We have also found, very recently, an efficient method for the synthesis of an important chiral ligand, *trans*-(*R,R*)-cyclohexanediamine **22**, through ring opening of a chiral aziridine **19** by TMS-N_3 even in the absence of Lewis acid catalysts. The diastereomers **20** and **21** were separable by column chromatography. The major diasteremer **20** on hydrogenation using 10% $Pd(OH)_2$ on activated charcoal gave **22** in 90% yield and ee > 99% (Scheme 1.12).[43]



Scheme 1.12

1.2 Background:

During our synthesis towards (+)-diplodialide A (**123** A, Part A, Chapter 3), we found that the β-ketoester **23** could be transformed to its corresponding thioacetal **24** in an excellent yield by using $Cu(OTf)_2$ as a catalyst (Scheme 1.13). This prompted us to investigate this reaction further in detail.



Scheme 1.13

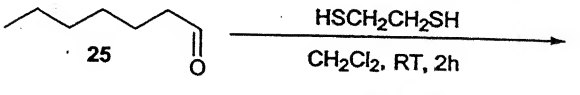
Since, solid supported reactions have attracted many synthetic organic chemists in recent years, because of simple workup procedures,[44] we became interested in developing this methodology (thioacetalization) using solid supported catalysts under solvent free conditions. We used $Cu(OTf)_2$ dispersed on SiO_2 as a solid acid catalyst for this transformation. A variety of aldehydes and ketones were transformed to their corresponding thioketals under this condition. During the progress of this work, we also found that silica gel efficiently catalyzed the aziridine ring opening reaction with aromatic amines and the results will be discussed in this chapter.

1.3 Present Work:

$Cu(OTf)_2$ is one of the most widely used Lewis acids in organic synthesis.[45] We have utilized $Cu(OTf)_2$ as a Lewis acid for important transformation like cleavage of epoxides with aromatic amines,[46] TMS-CN addition to carbonyl compounds,[47] Friedal-Crafts reaction,[48] acylation of alcohols,[49] allylation of carbonyl compounds[50] and conversion of TBDMS ethers to their corresponding acetates.[51] This prompted us to use this catalyst for thioacetalization reaction. Since solid supported Lewis acid catalyzed solvent free reactions have lots of advantages over solution phase chemistry,[44] we performed this transformation using silica gel supported $Cu(OTf)_2$ as a catalyst under solvent free conditions (SFC).

The catalyst $Cu(OTf)_2$-SiO_2 was prepared by mixing $Cu(OTf)_2$ (2 mmol) with 20 g of activated silica gel (activated at 120 °C under 1 mm of Hg for 6 h) and mechanically rotated for 12 h. Initially, we tried solution phase thioacetalization reaction using heptanal as a model substrate. Thus, treatment of heptanal **25** with 2 equivalent of 1,2-ethanedithiol in the presence of 5 mol% $Cu(OTf)_2$-SiO_2 in CH_2Cl_2 provided the desired thioacetal **26** in 90% yield. The same reaction when we carried out under solvent free conditions, by shaking mechanically the aldehyde and 1,2-ethanedithiol mixture with 500 mg of $Cu(OTf)_2$-SiO_2 (5 mol%) at rt, gave the thioacetal in 93% yield (Scheme 1.14). It was observed that $Cu(OTf)_2$ itself efficiently catalyzed thioacetalization of heptanal **25** in CH_2Cl_2 solvent, but the yield of the product **26** was a bit inferior (87%). By using simple SiO_2

as a catalyst, we did not observe any thioacetal formation under solvent free conditions even after several hours (Scheme 1.14).



Catalyst	Yield
$Cu(OTf)_2$	87%
$Cu(OTf)_2$-SiO_2	90%
$Cu(OTf)_2$-SiO_2 Without Solvent	93%
SiO_2	No Reaction

Scheme 1.14

Since, thioacetalization of **25** was very efficient under solvent free condition, we used the same condition for further investigation. Using 2 equivalent of 1,2-ethanedithiol and 5 mol% of the catalyst, a variety of aldehydes (Figure 1.3) and ketones (Figure 1.4) could be transformed to their corresponding thioacetals and thioketals respectively.[52] Aldehydes reacted faster than ketones as expected. Ketone group of a β-keto ester **38** could also be thioacetalized in a clean manner. Although the reaction was very clean in most of the cases, hindered and less reactive ketones such as benzophenone and camphor did not react with 1,2-ethanedithiol under solvent free conditions. But it could be affected by doing the reaction in toluene at 80 °C using 4 equivalent of 1,2-ethanedithiol. Thus, **43** and **44** were obtained in 98%

and 91% yields respectively, in toluene at 80 °C using catalytic amounts of $Cu(OTf)_2$-SiO_2.

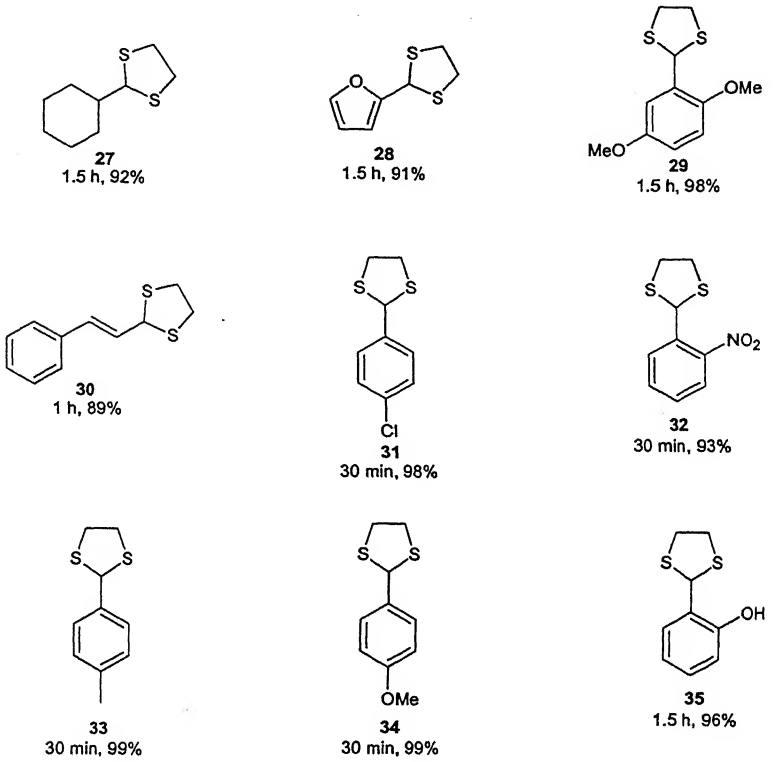


Figure 1.3

In the case of substrates containing aldehyde and ketone functionalities, some chemoselectivity was observed. For example, the keto aldehyde **45** on thioacetalization under standard condition gave a mixture of products **46** and **47** in 54% and 21% yields (ratio 2.6:1) respectively (Scheme 1.15).

It was also observed that the thioacetalization reaction could also be catalyzed using $CuCl_2$-SiO_2 in a solvent free condition, but the

reaction was slow and the yield was a bit inferior. For example, 4-*t*-butyl cyclohexanone was converted into its thioacetal **40** in 88% yield after 8 h using $CuCl_2.SiO_2$.

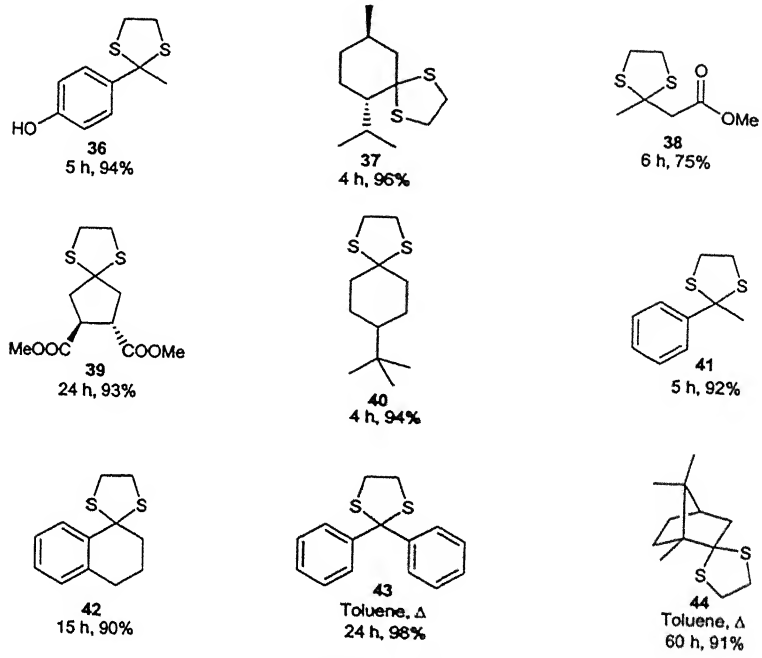
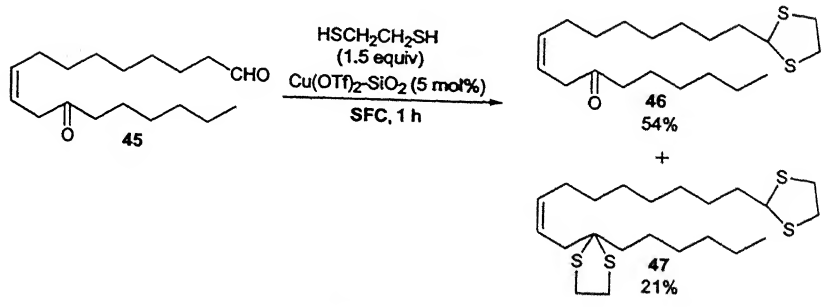
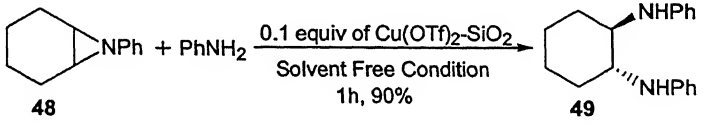


Figure 1.4



Scheme 1.15

The main advantages of the above method include easier handling, milder reaction conditions, simple workup procedures and most importantly, environmental friendly. While working on the thioacetalization reaction, we envisioned that aziridines could also be cleaved with amines under the same solvent free conditions. We have already reported solution phase aziridine ring opening reaction with a variety of nuclecphiles, which include aromatic amines[53] and alcohols.[54] In a standard experiment, we treated the *N*-phenyl aziridine **48** with 1.2 equivalent of aniline in the presence of 10 mol% of $Cu(OTf)_2$-SiO_2 under solvent free condition. It was heartening to see that the product **49** was obtained in 90% yield within an hour (Scheme 1.16).



Scheme 1.16

Since silica gel itself has shown to be the most useful inorganic solid for effecting a variety of functional group transformation,[55] we were interested to perform the above reaction with only SiO_2 under solvent free conditions. Thus, we exposed *N*-phenyl aziridine **48** to 1.2 equivalent of aniline for an hour in the presence of activated SiO_2 (activated at 120 °C under 1 mm of Hg for 6 h) under solvent free conditions. It was surprising to see that the product **49** was obtained in 91% yield after just filtration of the reaction mixture. So, we used the above condition for further elaboration. A variety of aziridines were

prepared from their corresponding amino alcohols in one step using MsCl (1.1 equiv) and Et_3N (2.5 equiv) in pyridine (as solvent) at room temperature.[56] The opening of *N*-phenylcyclohexeneimine **48** was tried with a variety of aromatic amines (1.2 equiv) using activated SiO_2 (500 mg for 1 mmol of aziridine) as a catalyst at room temperature under solvent free conditions (Figure 1.5).[57]

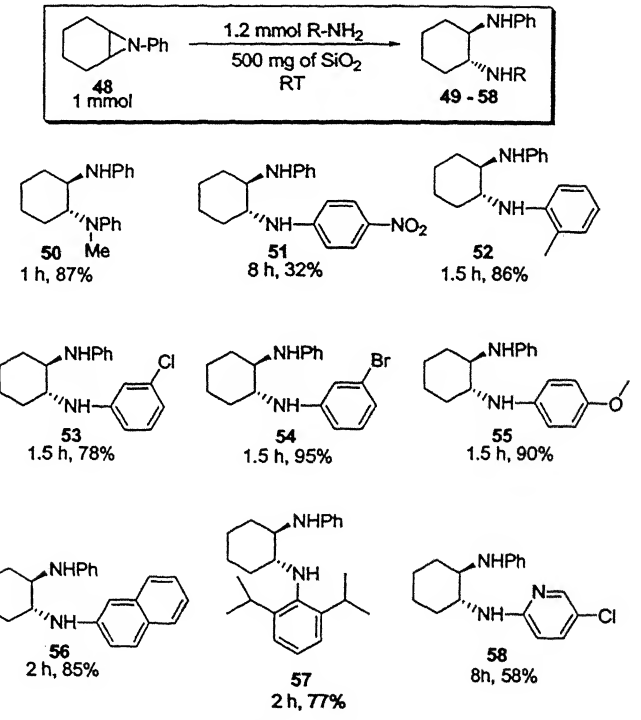


Figure 1.5

In all the cases, a very clean reaction was observed and the *trans* stereochemistry of diamines was deduced from the relevant coupling constants. The aziridine opening reaction tolerated a varying degree of steric hindrance on aromatic amines such as *o,o*-

diisopropylaniline **57**. The worthy feature of the reaction is that even highly deactivated amines such as *p*-nitroaniline also opened the aziridines in moderate yields (**51**, Figure 1.5).

In order to show the scope of the reaction, this methodology was extended to a variety of cyclic and acyclic aziridines (Table 1.1). In almost all the cases, a high yield of the opened product was obtained. In the case of acyclic terminal aziridines, the reaction was highly regioselective. For example, in the case of **65** only one product was isolated, and it was due to the attack of the aromatic amine at the less hindered terminal carbon atom (entry 7, Table 1.1). In the case of 2-phenyl aziridine **66** (entry 8, Table 1.1), the product formed was the one due to attack of aromatic amines at the benzylic carbon atom (internal attack). The aziridine opening reaction was smooth in a disubstituted acyclic substrate **64** (entry 6, Table 1.1). It is remarkable that unactivated aziridines could be opened with aromatic amines under very mild conditions. This kind of result is quite unprecedented in the literature for aziridine chemistry.

Another unusual feature of this reaction is that only aromatic amines opened the aziridines. Aliphatic amines such as, diethylamine, *n*-butyl amine, benzylamine and pyrrolidine failed to react with aziridines at room temperature, even after 2 days, under solvent free conditions. This was further conformed by the treatment of aziridine **48** with a mixture of aniline and benzyl amine. Only aniline opened product was obtained in 81% yield after 1 h under SiO_2 catalyzed solvent free conditions (Scheme 1.17).

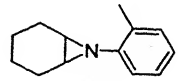
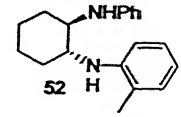
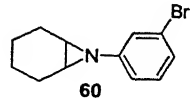
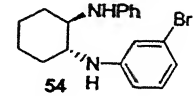
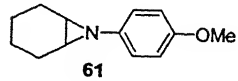
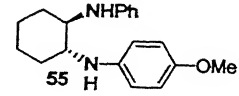
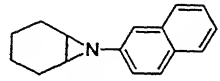
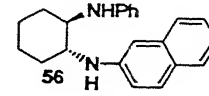
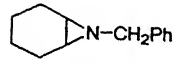
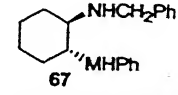
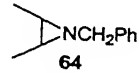
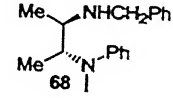
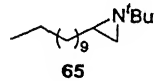
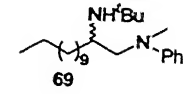
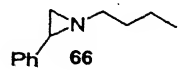
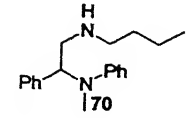
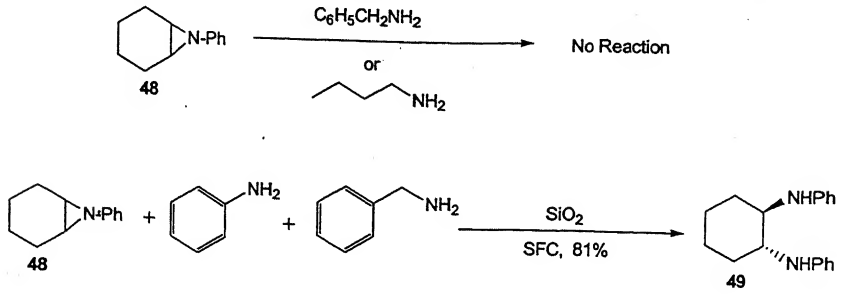
Entry	Aziridine	Product	Time	Isolated Yield (%)
1.	 **59**	 **52**	1 h	75%
2.	 **60**	 **54**	2 h	70%
3.	 **61**	 **55**	1 h	89%
4.	 **62**	 **56**	5 h	66%
5.	 **63**	 **67**	2 h	91%
6.	 **64**	 **68**	24 h	45%
7.	 **65**	 **69**	10 h	39%
8.	 **66**	 **70**	48 h	89%

Table 1.1



Scheme 1.17

In conclusion, we discovered that $Cu(OTf)_2$-SiO_2 is an efficient catalyst for thioacetalization of carbonyl compounds under solvent free conditions. A variety of aldehydes and ketones could be transformed to their corresponding thioacetals under these conditions. We also found that SiO_2 efficiently catalyses the aminolysis of nonactivated aziridines under solvent free conditions. This method was found to be selective for only aromatic amines. Highly deactivated amines such as *p*-nitroaniline also cleaved the aziridines under these conditions.

1.4. Experimental Section

General Methods and Materials:

^{1}H NMR spectra were recorder on JEOL PMX 300 and JEOL-60 series of instruments using solutions in $CDCl_3$ and CCl_4. 1,2-ethanedithiol, mathanesulfonyl chloride and all the aldehydes, ketones and amines used were obtained from Fluka and Lancaster and used as received. All amino acids used for the synthesis of aziridines were prepared by known procedures.[56]

Preparation of $Cu(OTf)_2$-SiO_2. A mixture of $Cu(OTf)_2$ (2 mmol) and activated SiO_2 [activated at 120 °C at 1mm Hg for 6 h] (20 g) was taken in a 250 mL round bottom flask. The flask was stoppered with a septum and tied with the rod of a rotary evaporator. It was rotated for 3 h and used for thioacetalization reactions.

General procedure for thioacetalization reaction. A mixture of carbonyl compound (1 mmol), 1,2-ethanedithiol (2 mmol) and $Cu(OTf)_2$-SiO_2 (500 mg, 0.05 mmol) was taken in a 5 mL round bottom flask. The flask was stoppered with a septum and tied with the rod of a rotary evaporator. It was rotated till the reaction was complete. The whole mixture was loaded over a silica gel column and eluted with EtOAc in petroleum ether to obtain a pure thioacetal.

2-Hexyl-[1,3]dithiolane 26.[75b] Yield 93%; colorless liquid; R_f 0.90 (1% EtOAc in petroleum ether); ^{1}H NMR (60 MHz, CCl_4) δ 0.80 (t, J = 6.0 Hz, 3H), 1.20-1.80 (m, 10H), 3.10 (s, 4H), 4.3 (t, J = 6.0 Hz, 1H).

2-Cyclohexyl-[1,3]dithiolane 27.[75a] Yield 92%; colorless liquid; R_f 0.90 (2% EtOAc in petroleum ether); ^{1}H NMR (60 MHz, CCl_4) δ 1.10-2.0 (m, 11H), 3.1 (s, 4H), 4.3 (d, J = 6.0 Hz, 1H).

2-[1,3]Dithiolan-2-yl-furan 28.[75b] Yield 91%; brown paste; R_f 0.90 (5% EtOAc in petroleum ether); ^{1}H NMR (60 MHz, CCl_4) δ 3.30 (s, 4H), 5.50 (s, 1H), 6.10- 6.25 (m, 2H), 7.20- 7.30 (m, 1H).

2-(2,5-Dimethoxy-benzyl)-[1,3]dithiolane 29. Yield 98%; white solid; mp 92-95 °C; R_f 0.75 (5% EtOAC in petroleum ether); ^{1}H NMR (60 MHz, CCl_4) δ 3.25 (s, 4H), 3.65 (s, 3H), 3.75 (s, 3H), 5.85 (s, 1H), 6.60 (d, J = 3.0 Hz, 2H), 7.20 (s, 1H).

2-Styryl-[1,3]dithiolane 30.[75b] Yield 89%; brown solid; mp 56-58 °C; R_f 0.85 (5% EtOAc in petroleum ether); ^{1}H NMR (60 MHz, CCl_4) δ 3.30 (s, 4H), 5.15 (d, J = 9.0 Hz, 1H), 5.9- 6.60 (m, 2H), 7.10-7.35 (m, 5H).

2-(4-Chloro-phenyl)-[1,3]dithiolane 31.[75b] Yield 98%; white solid; mp 62-64 °C; R_f 0.65 (5% EtOAc in petroleum ether); ^{1}H NMR (60 MHz, CCl_4) δ 3.38 (s, 4H), 5.61 (s, 1H), 7.08 (d, J = 9.0 Hz, 2H), 7.52 (d, J = 9.0 Hz, 2H).

2-(2-Nitro-phenyl)-[1,3]dithiolane 32. Yield 93%; yellow solid; mp 64-66 °C; R_f 0.80 (5% EtOAc in petroleum ether); ^{1}H NMR (60 MHz, CCl_4) δ 3.50 (s, 4H), 5.65 (s, 1H), 7.35- 8.40 (m, 4H).

2-*p*-Tolyl-[1,3]dithiolane 33.[75b] Yield 99%; pale yellow solid; mp 57-59 °C R_f 0.95 (5% EtOAc in petroleum ether); ^{1}H NMR (60 MHz, CCl_4) δ 2.30 (s, 3H), 3.35 (d, J = 3.0 Hz, 4H), 5.50 (s, 1H), 7.0 (d, J = 9.0 Hz, 2H), 7.45 (d, J = 9.0 Hz, 2H).

2-(4-Methoxy-phenyl)-[1,3]dithiolane 34. Yield 99%; white solid; mp 60-62 °C; R_f 0.85 (5% EtOAc in petroleum ether); ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.31- 3.55 (m, 4H), 3.79 (s, 3H), 5.63 (s, 1H), 6.83 (d, J = 8.6 Hz, 2H), 7.45 (d, J = 8.6 Hz, 2H).

2-[1,3]Dithiolan-2-yl-phenol 35. Yield 96%; white solid 72-74 °C; R_f 0.45 (10% EtOAc in petroleum ether); ^{1}H NMR (60 MHz, CCl_4) δ 3.0-3.65 (m, 4H), 5.80 (s, 1H), 6.70- 7.35 (m, 4H).

4-(2-Methyl-[1,3]dithiolan-2-yl)-phenol 36. Yield 94%; white solid 78-80 °C; R_f 0.50 (10% EtOAc in petroleum ether); ^{1}H NMR (60 MHz, CCl_4) δ 2.05 (s, 3H), 3.30 (s, 4H), 6.55 (d, J = 9.0 Hz, 2H), 7.45 (d, J = 9.0 Hz, 2H).

6-Isopropyl-9-methyl-1,4-dithia-spiro[4.5]decane 37. Yield 96%; semisolid; R_f 0.95 (1% EtOAc in petroleum ether); ^{1}H NMR (60 MHz, CCl_4) δ 0.88 (d, J = 9.0 Hz, 9H), 1.25- 2.60 (m, 8H), 3.20 (s, 4H).

(2-Methyl-[1,3]dithiolan-2-yl)-acetic acid methyl ester 38. Yield 75%; white semisolid; R_f 0.85 (10% EtOAc in petroleum ether); FT IR ($CHCl_3$ solution) 1742 cm^{-1}; ^{1}H NMR (60 MHz, CCl_4) δ 0.90 (s, 3H), 2.90 (s, 2H), 3.30 (s, 4H), 3.65 (s, 3H).

1,4-Dithia-spiro[4.4]nonane-7,8-dicarboxylic acid dimethyl ester 39. Yield 93%; colorless liquid; R_f 0.70 (2% EtOAc in petroleum ether); FT IR (neat) 1739 cm^{-1}; ^{1}H NMR (60 MHz, CCl_4) δ 2.40 (t, J = 3.0 Hz, 2H), 2.55 (d, J = 3.0, 4H), 3.30 (s, 4H), 3.70 (s, 6H).

8-*tert*-Butyl-1,4-dithia-spiro[4.5]decane 40. Yield 94%; white solid; mp 60-62 °C; R_f 0.90 (1% EtOAc in petroleum ether); ^{1}H NMR (60 MHz, CCl_4) δ 1.0 (s, 9H), 1.20- 2.20 (m, 9H), 3.35 (s, 4H).

2-Methyl-2-phenyl-[1,3]dithiolane 41.[75b] Yield 92%; white solid; mp 82-84 °C; R_f 0.90 (1% EtOAc in petroleum ether); ^{1}H NMR (60 MHz, CCl_4) δ 2.10 (s, 3H), 3.35 (s, 4H), 7.05- 7.80 (m, 5H).

Tetralone thioacetal 42: Yield 90%; white solid; mp 54-56 °C; R_f 0.90 (2% EtOAc in petroleum ether); ^{1}H NMR (60 MHz, CCl_4) δ 1.85-2.50 (m, 4H), 2.75 (t, J = 6.0 Hz, 2H), 3.40-3.55 (m, 4H), 6.80-7.85 (m, 4H).

2,2-Diphenyl-[1,3]dithiolane 43.[75b] $Cu(OTf)_2$-SiO_2 (500 mg, 0.05 mmol) was added to a solution of 1,2-ethanedithiol (188 µL, 2 mmol) and benzophenone (91 mg, 0.5 mmol) in *anhydrous* toluene (4 mL) and the resulting suspension was refluxed for 24 h. It was filtered and washed with $CHCl_3$. Evaporation of the solvent followed by silica gel column chromatography using neat petroleum ether gave the pure compound **43**. Yield 254 mg (98%); white solid; mp 80-82 °C; R_f 0.90 (neat petroleum ether); ^{1}H NMR (60 MHz, CCl_4) δ 3.18 (s, 4H), 6.90-7.54 (m, 10 H).

Camphor thioketal 44.[75b] $Cu(OTf)_2$-SiO_2 (500 mg, 0.05 mmol) was added to a solution of 1,2-ethanedithiol (188 µL, 2 mmol) and camphor (76 mg, 0.5 mmol) in *anhydrous* toluene (4 mL) and the resulting suspension was refluxed for 24 h. It was filtered and washed with $CHCl_3$. Evaporation of the solvent followed by silica gel column chromatography using neat petroleum ether gave the pure compound **44**. Yield 207 mg (91%); white solid; mp 58-61 °C; R_f 0.85 (neat petroleum ether); ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.90 (s, 3H), 1.03 (s, 6H), 1.22-1.37 (m, 1H), 1.58-1.76 (m, 3H), 1.96 (d, J = 10.7 Hz, 1H),

2.22 (d, J = 14.0 Hz, 1H), 2.61 (td, J = 14.0, 3.2 Hz, 1H), 2.98-3.39 (m, 4H).

18-[1,3]Dithiolan-2-yl-octadec-9-en-7-one 46. Yield 54%; colorless oil; R_f 0.25 (2% EtOAc in petroleum ether); FT IR (neat) 1709 cm^{-1}; ^{1}NMR (60 MHz) δ 0.90 (t, J = 6.0 Hz, 3H), 1.10-1.55 (m, 24 H), 1.90-2.20 (m, 2H), 2.40 (t, J = 6.0 Hz, 2H), 3.05 (d, J = 6.0 Hz, 2H), 3.25 (s, 4H), 4.40 (t, J = 6.0 Hz, 1H), 5.55 (t, J = 6.0 Hz, 2H).

2-(10-[1,3]Dithiolan-2-yl-dec-2-enyl)-2-hexyl-[1,3]dithiolane 47. Yield 21%; colorless oil; R_f 0.60 (2% EtOAc in petroleum ether); ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.88 (t, J = 6.5 Hz, 3H), 1.29- 1.58 (m, 21 H), 1.76- 2.07 (m, 6H), 2.68 (d, J = 5.3 Hz, 2H), 3.22 (d, J = 3.1 Hz, 4H), 3.28 (s, 4H), 4.47 (t, J = 7.0 Hz, 1H), 5.49 (q, J = 5.2 Hz, 2H).

General procedure for the Synthesis of Aziridines from β-Amino Alcohols. Methanesulfonyl chloride (5.5 mmol) was added drop-wise to a mixture of β-amino alcohol (5 mmol) and Et_3N (12.5 mmol) in pyridine (6 mL) at 0 °C under nitrogen atmosphere. The resulting brown colored solution was stirred overnight at room temperature. The reaction mixture was diluted with CH_2Cl_2 and washed with water. The organic layer was dried over *anhydrous* Na_2SO_4 and the solvent was removed by rotary evaporator. Purification over silica gel column gave pure aziridines.

***N*-Phenylcyclohexeneimine 48.**[56] Yield 84%; colorless liquid; R_f 0.42 (2% EtOAc in petroleum ether); IR (neat) 2925, 1583 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.32 (m, 2H), 1.51 (m, 2H), 1.94 (m, 2H), 2.05 (m, 2H), 2.33 (m, 2H), 6.97 (m, 3H), 7.22 (m, 2H); ^{13}C NMR (75 MHz,

$CDCl_3$) δ 20.32, 24.62, 38.59, 120.32, 121.73, 128.24, 155.61; LCMS (APCI, *m/z*) 174 (M^+ +1).

***N-o*-Methylphenylcyclohexeneimine 59.**[56] Yield 65%; colorless liquid; R_f 0.50 (2% EtOAc in petroleum ether); IR (neat) 2940, 1593 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.38 (m, 2H), 1.58 (m, 2H), 1.98 (m, 2H), 2.1 (m, 2H), 2.29 (m, 2H), 2.34 (s, 3H), 6.58 (m, 2H), 7.1 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.72, 20.41, 24.33, 38.48, 119.07, 121.76, 126.25, 130.36, 130.57, 152.95.

***N-m*-Bromophenylcyclohexeneimine 60.**[56] Yield 43%; colorless solid; mp 42-43 °C; R_f 0.55 (2% EtOAc in petroleum ether); IR (KBr) 2935, 1580 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.22 (m, 2H), 1.45 (m, 2H), 1.90 (m, 2H), 2.00 (m, 2H), 2.30 (m, 2H), 6.88 (m, 1H), 7.08 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.22, 24.46, 38.97, 119.14, 122.32, 123.51, 124.77, 130.12, 157.19.

***N-p*-Methoxyphenylcyclopenteneimine 61.**[56] Yield 73%; colorless solid; mp 33-34 °C; R_f 0.50 (2% EtOAc in petroleum ether); IR (KBr) 2945, 1500 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.28 (m, 2H), 1.46 (m, 2H), 1.90 (m, 2H), 2.0 (m, 2H), 2.24 (m, 2H), 3.74 (s, 3H), 6.75 (d, J = 8.7 Hz, 2H), 6.9 (d, J = 9.0 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$,) δ 20.35, 24.63, 38.86, 55.47, 114.08, 121.08, 149.03, 154.64.

***N-β*-Naphthylcyclohexeneimine 62.**[56] Yield 63%; colorless solid; R_f 0.65 (2% EtOAc in petroleum ether); ^1H NMR (300 MHz, $CDCl_3$) δ 1.35 (m, 2H), 1.58 (m, 2H), 2.0 (m, 2H), 2.12 (m, 2H), 2.42 (m, 2H), 7.25 (m, 2H), 7.32 (m, 1H), 7.42 (m, 1H), 7.71 (m, 3H); ^{13}C NMR (75

MHz, $CDCl_3$) δ 20.38, 24.66, 38.86, 115.35, 122.06, 123.73, 126.13, 126.56, 127.60, 128.62, 129.77, 134.14, 153.36.

***N*-Benzylcyclohexeneimine 63.**[56] Yield 51%; colorless liquid; R_f 0.28 (2% EtOAc in petroleum ether); IR (neat) 2920, 1585 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.20 (m, 2H), 1.40 (m, 2H), 1.63 (m, 2H), 1.80 (m, 2H), 1.85 (m, 2H), 3.48 (s, 2H), 7.3 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.55, 24.43, 38.46, 64.27, 126.51, δ 127.37, 128.14; LCMS (APCI, *m/z*) 188 (M^+ +1).

***N*-Benzyl-2,3-dimethylaziridine 64.**[56] Yield 49%; colorless liquid; R_f 0.34 (5% EtOAc in petroleum ether); IR (neat) 2940, 1575 cm^{-1}; ^1H NMR (60 MHz, CCl_4) δ 1.15 (d, J = 5.0 Hz, 6H), 1.50 (m, 2H), 3.55 (s, 2H), 7.4 (m, 5H).

***N*-*n*-Butyl-2-phenylaziridine 66.**[56] Yield 43%; colorless liquid; R_f 0.61 (5% EtOAc in petroleum ether); IR (neat) 2950, 1598 cm^{-1}; ^1H NMR (60 MHz, CCl_4) δ 0.93 (t, J = 6.0 Hz, 3H) 1.55 (m, 5H), 1.70 (m, 1H), 2.3 (m, 3H), 7.3 (m, 5H).

General Procedure for Aziridine Opening with Aromatic Amines under solvent free conditions. A mixture of an aziridine (1 mmol), an aromatic amine (1.2 mmol) and silica gel (500 mg; activated at 120 °C under vacuum for 6 h) was taken in a 5 mL R.B. flask and the solid shaken till the reaction was complete (disappearance of aziridine spot on TLC plate). The silica gel-reaction mixture was directly loaded onto a small silica gel column and eluted with ethyl acetate-petroleum ether to afford the pure diamines.

***trans*-*N*,*N'*-Diphenyl-1,2-cyclohexanediamine 49.**[42] Yield 91%; colorless gel; *Rf* 0.4 (2% EtOAc in petroleum ether); IR (neat) 3390 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.23 (m, 2H), 1.42 (m, 2H), 1.8 (m, 2H), 2.39 (m, 2H), 3.24 (m, 2H), 3.92 (bs, 2H, N*H*), 6.62 (d, J = 7.0 Hz, 4H), 6,75 (t, J = 7.0 Hz, 2H), 7.21 (dd, J = 7.0 Hz, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.6, 32.5, 57.2, 113.47, 117.54, 129.3, 147.7; LCMS (APCI, *m/z*) 267 (M^++1).

***trans*-*N*-Phenyl-(*N'*-methyl-*N'*-phenyl)-1,2-cyclohexanediamine 50.**[42] Yield 87%; viscous liquid; R_f 0.50 (2% EtOAc in petroleum ether); IR (neat) 3400 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.2-1.6 (bm, 4H), 1.82 (m, 3H), 2.42 (m, 1H), 2.66 (s, 3H), 3.31 (ddd, J = 10.2, 10.2, 3.6 Hz, 1H), 3.64 (m, 1H), 4.0 (bs, N*H*, 1H), 6.58 (m, 2H), 6.7 (m, 1H), 6.78 (m, 1H), 6.84 (m, 2H), 7.15 (m, 2H), 7.27 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.6, 25.7, 27.8, 30.7, 33.5, 55.2, 62.9, 113.2, 114.0, 117.2, 117.3, 129.2, 129.2, 147.8, 150.8; LCMS (APCI, *m/z*) 281 (M^++1).

***trans*-*N*-Phenyl-*N'*-(*p*-nitrophenyl)cyclohexanediamine 51.**[42] Yield 32%; pale yellow solid; mp 145 °C; R_f 0.80 (25% EtOAc in petroleum ether); IR (KBr) 3350 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.22 - 1.6 (bm, 4H), 1.80 (m, 2H), 2.30 (m, 2H), 3.28 (m, 2H), 3.56 (bs, N*H*, 1H), 4.63 (bs, 1H, N*H*), 6.48 (m, 2H), 6.58 (m, 2H), 6.7 (m, 1H), 7,15 (m, 2H), 8.02 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.4, 24.6, 32.2, 32.6, 56.9, 57.4, 111.5, 113.4, 118.0, 126.4, 129.5, 138.0, 147.1, 152.9; LCMS (APCI, *m/z*) 312 (M^++1).

***trans*-*N*-Phenyl-*N'*-(*o*-methylphenyl)-1,2-cyclohexanediamine 52.**[42] Yield 86%; white solid; mp 70-71 °C; R_f 0.42 (2% EtOAc in petroleum ether); IR (KBr) 3390 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.30 (m, 2H), 1.50 (m, 2H), 1.82 (m, 2H), 2.05 (s, 3H), 2.41 (m, 2H), 3.28 (ddd, J = 9.6, 9.6, 3.6 Hz, 1H), 3.37 (ddd, J = 9.9, 9.9, 3.9 Hz, 1H), 3.93 (bs, 2H, N*H*), 6.71 (m, 5H), 7.1 (d, J = 7.5 Hz, 1H), 7.23 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.5, 24.6, 24.7, 32.6, 32.7, 57.3, 57.7, 110.2, 113.7, 117.1, 117.7, 122.9, 127.0, 129.3, 130.3, 145.6, 147.5; LCMS (APCI, *m/z*) 281 (M^+ + 1).

***trans*--*N*-Phenyl-*N'*-(*m*-chlorophenyl)-1,2-cyclohexanediamine 53.**[42] Yield 78%; semisolid; R_f 0.39 (2% EtOAc in petroleum ether); IR (KBr) 3390 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.24 (m, 2H), 1.40-1.43 (m, 2H), 1.79-1.83 (m, 2H), 2.37-2.39 (m, 2H), 3.19-3.21 (m, 2H), 3.84 (bs, 2H, N*H*), 6.52-6.53 (m, 1H), 6.63 (d, J = 8.5 Hz, 2H), 6.73-6.76 (m, 2H), 6.84-6.86 (m, 1H), 7.02-7.05 (m, 1H), 7.19-7.22 (m, 2H).

***trans*-*N*-Phenyl-*N'*-(*m*-bromophenyl)-1,2-cyclohexanediamine 54.**[42] Yield 95%; semisolid; R_f 0.39 (2% EtOAc in petroleum ether); IR (KBr) 3390 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.22 (m, 2H), 1.45(m, 2H), 1.81 (m, 2H), 2.38 (m, 2H), 3.19 (m, 2H), 3.82 (bs, 2H, N*H*), 6.52 (m, 1H), 6.65 (d, J = 8.5 Hz, 2H), 6.75 (m, 2H), 6.84 (m, 1H), 7.02 (m, 1H), 7.21 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.5, 24.6, 32.3, 32.5, 57.0, 57.2, 112.2, 113.5, 115.7, 117.7, 120.1, 123.3, 129.3, 130.5, 147.5, 149.0;

***trans*-*N*-Phenyl-*N'*-(*p*-methoxyphenyl)-1,2-cyclohexanediamine 55.**[42] Yield 90%; colorless gel; R_f 0.30 (2% EtOAc in petroleum ether):

IR (neat) 3365 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.22 (m, 2H), 1.42 (m, 2H), 1.78 (m, 2H), 2.34 (m, 2H), 3.11 (ddd, J = 9.6, 9.6, 3.3 Hz, 1H), 3.20 (ddd, J = 9.6, 9.6, 3.3 Hz, 1H), 3.70 (bs, 2H, N*H*), 3.76 (s, 3H), 6.63 (m, 4H), 6.71 (m, 1H), 6.79 (m, 2H), 7.19 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.6, 32.6, 55.8, 57.4, 58.4, 113.6, 115.0, 115.3, 117.6, 129.3, 141.8, 147.8, 152.4. LCMS (APCI, *m/z*) 297 (M^++1).

***trans*-*N*-Phenyl-*N'*-(β-naphthyl)-1,2-cyclohexanediamine 56.**[42] Yield 85%; semisolid; R_f 0.42 (2% EtOAc in petroleum ether); IR (KBr) 3380 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.3 (m, 2H), 1.5 (m, 2H), 1.82 (m, 2H), 2.42 (m, 2H), 3.32 (m, 2H), 3.98 (bs, 2H, N*H*), 6.62 (m, 2H), 6.78 (m, 1H), 6.82 (m, 2H), 7.20 (m, 3H), 7.40 (m, 1H), 7.64 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.6, 24.6, 32.2, 32.5, 57.15, 57.22, 104.8, 113.5, 117.6, 118.5, 122.0, 125.8, 126.4, 127.5, 127.6, 129.0, 129.3, 135.1, 145.3, 147.6; LCMS (APCI, *m/z*) 317 (M^++1).

***trans*-*N*-Phenyl-[*N'*-(2,5-diisopropylphenyl)-1,2-cyclohexane diamine 57.**[42] Yield 77%; viscous liquid; R_f 0.45 (2% EtOAc in petroleum ether); IR (neat) 3360, 3400 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ 1.15 (d, J = 5.5 Hz, 6H), 1.25 (d, J = 5.5 Hz, 6H), 1.3 - 2.4 (m, 8H), 2.93 - 3.2 (m, 4H), 3.27 (q, J = 7.0 Hz, 2H), 6.75 (m, 2H), 7.0 - 7.4 (m, 6H).

2-*N*-(*trans*-2'-Aminophenyl cyclohexyl)-5-chloro pyridine 58.[42] Yield 58%; mp 89-90 °C; R_f 0.62 (10% EtOAc in petroleum ether); IR (KBr) 3400 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.25 (m, 4H), 1.78 (m, 2H), 2.2 (m, 1H), 2.28 (m, 1H), 3.13 (m, 2H), 3.81 (m, 1H), 4.37 (m,

IR (neat) 3365 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.22 (m, 2H), 1.42 (m, 2H), 1.78 (m, 2H), 2.34 (m, 2H), 3.11 (ddd, J = 9.6, 9.6, 3.3 Hz, 1H), 3.20 (ddd, J = 9.6, 9.6, 3.3 Hz, 1H), 3.70 (bs, 2H, N*H*), 3.76 (s, 3H), 6.63 (m, 4H), 6.71 (m, 1H), 6.79 (m, 2H), 7.19 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.6, 32.6, 55.8, 57.4, 58.4, 113.6, 115.0, 115.3, 117.6, 129.3, 141.8, 147.8, 152.4. LCMS (APCI, *m/z*) 297 (M^++1).

***trans*-*N*-Phenyl-*N'*-(β-naphthyl)-1,2-cyclohexanediamine 56.**[42] Yield 85%; semisolid; R_f 0.42 (2% EtOAc in petroleum ether); IR (KBr) 3380 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.3 (m, 2H), 1.5 (m, 2H), 1.82 (m, 2H), 2.42 (m, 2H), 3.32 (m, 2H), 3.98 (bs, 2H, N*H*), 6.62 (m, 2H), 6.78 (m, 1H), 6.82 (m, 2H), 7.20 (m, 3H), 7.40 (m, 1H), 7.64 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.6, 24.6, 32.2, 32.5, 57.15, 57.22, 104.8, 113.5, 117.6, 118.5, 122.0, 125.8, 126.4, 127.5, 127.6, 129.0, 129.3, 135.1, 145.3, 147.6; LCMS (APCI, *m/z*) 317 (M^++1).

***trans*-*N*-Phenyl-[*N'*-(2,5-diisopropylphenyl)-1,2-cyclohexane diamine 57.**[42] Yield 77%; viscous liquid; R_f 0.45 (2% EtOAc in petroleum ether); IR (neat) 3360, 3400 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ 1.15 (d, J = 5.5 Hz, 6H), 1.25 (d, J = 5.5 Hz, 6H), 1.3 - 2.4 (m, 8H), 2.93 - 3.2 (m, 4H), 3.27 (q, J = 7.0 Hz, 2H), 6.75 (m, 2H), 7.0 - 7.4 (m, 6H).

2-*N*-(*trans*-2'-Aminophenyl cyclohexyl)-5-chloro pyridine 58.[42] Yield 58%; mp 89-90 °C; R_f 0.62 (10% EtOAc in petroleum ether); IR (KBr) 3400 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.25 (m, 4H), 1.78 (m, 2H), 2.2 (m, 1H), 2.28 (m, 1H), 3.13 (m, 2H), 3.81 (m, 1H), 4.37 (m,

1H), 6.24 (m, 1H), 6.48 (m, 2H), 6.62 (m, 1H), 7.05 (m, 2H), 7.26 (m, 1H), 8.05 (m, 1H).

***trans*-*N*-Phenyl-*N'*-benzyl-1,2-cyclohexanediamine 67.**[42] Yield 91%; mp 68-70 °C; R_f 0.58 (25% EtOAc in petroleum ether); IR (KBr) 3295 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.10 (m, 1H), 1.23 (m, 3H), 1.70 (m, 2H), 2.10 (bs, 1H, N*H*), 2.18 (m, 2H), 2.33 (ddd, J = 9.9, 9.9, 4.2 Hz, 1H), 3.12 (ddd, J = 10.2, 10.2, 3.6 Hz, 1H), 3.37 (bs, 1H, N*H*) 3.80 (AB_q, J = 13.5 Hz, 2H), 6.64 (m, 3H), 7.13 (m, 2H), 7.25 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.6, 25.0, 31.4, 32.5, 50.7, 57.5, 60.8, 114.0, 117.7, 126.9, 128.1, 128.4,129.2, 140.6, 148.2; LCMS (APCI, *m/z*) 281 (M^++1).

***N*-Methyl-*N*-phenyl[3-benzylamino]butyl-2-amine 68.**[42] Yield 45%; Viscous liquid; R_f 0.32 (10% EtOAc in petroleum ether); IR (neat) 3300 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.02 (d, J = 6.6 Hz, 3H), 1.14 (d, J = 6.6 Hz, 3H), 2.30 (bs, 1H, N*H*), 2.50 (s, 3H), 2.73 (m, 1H), 3.67 (m, 1H), 3.81 (ABq, J = 13.5 Hz, 2H), 6.76 (t, J = 7.2 Hz, 1H), 6.8 (d, J = 8.1 Hz, 2H), 7.26 (m, 7H); MS (EI, *m/z*) 268 (M^+).

***N*-Methyl-*N*-phenyl[2-(*N*-t-butyl)amino]tridecenyl amine 69.**[42] Yield 39%; viscous liquid; R_f 0.15 (10% EtOAc in petroleum ether); IR (neat) 3380 cm^{-1}; 1H NMR (300 MHz, $CDCl_3$) δ 0.87 (t, J = 6.8 Hz, 3H), 1.05 (s, 9H), 1.25 (m, 18H), 1.36 (m, 2H), 2.89 (s, 3H), 2.94 (m, 1H), 3.19 (d, J = 6.0 Hz, 2H), 6.70 (m, 3H), 7.21 (m, 2H).

***N*-*n*-Butyl-[2-(*N'*methyl-*N'*-phenyl)amino]-2-phenylethylamine 70.**[42] Yield 89%; viscous liquid; R_f 0.65 (20% EtOAc in petroleum ether); IR (neat) 3300 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.89 (t, J =

7.2 Hz, 3H), 1.33 (m, 2H), 1.47 (m, 2H), 1.55 (bs, 1H, N*H*), 2.68 (m, 2H), 2.71 (s, 3H), 3.20 (d, J = 7.8 Hz, 2H), 5.16 (t, J = 6.6 Hz, 1H), 6.75 (t, J = 7.2 Hz, 1H), 6.89 (d, J = 8.1 Hz, 2H), 7.27 (m, 7H); MS (EI, *m/z*) 282 (M^+).

Chapter 2

Triphase Catalysis in Epoxidation of α,β-enones with Polymer Bound Quaternary Ammonium Salts

2.1 Introduction:

The development of cleaner and more efficient synthetic routes to minimize environmental damage has been approached in many ways. Amongst these are: improved catalytic methods, solvent free reactions, reactions employing water as the solvent, the application of supercritical fluids and atom efficient synthesis. In all of these cases, the focus is to reduce the amount of materials required to perform the desired synthetic step, to obtain products requiring the minimum amount of expense and complex purification steps, and therefore to reduce waste. By the use of solid supported reagents or catalysts, it is possible to achieve at least some of the above-mentioned objectives.[58]

The use of solid supported reagents in chemistry offers many potential environmental advantages compared to traditional reagents.[59] There has been extensive growth in the application of modified polymers, and polymers incorporating reactive functional groups as reagents in organic synthesis,[60] and the use of ion-exchange resins as catalysts.[61] The advantages of reagents or catalysts supported on ion-exchangers are potentially manifold and briefly comprise the following: (i) They can be employed in excess in order to drive the desired reaction to completion.

(ii) Contamination of the final product with reagent or reagent by-products is minimized.

(iii) Removal of the resin is easily achieved by filtration, thus greatly simplifying the reaction work-up.

(iv) The possibility of recycling the supported reagents or catalysts, thus minimizing waste.

The solid supported reagents or catalysts are clean, potentially re-usable and create less waste than conventional materials and, as such, represent reagents for 'Green Chemistry'.[1]

2.1.1 Triphase catalysis:

A significant and recurring problem in organic synthesis stems from the use of water-soluble reagent in chemically altering a water-insoluble organic substrate. If the reaction is conducted as a heterogeneous process (e.g., organic phase aqueous phase reaction), the observed reaction rates are normally very slow owing to the very low concentration of at least one of the reactants in each phase. One of the methods to circumvent this problem is the use of phase-transfer catalysts (PTC) (most commonly a tetraalkylammonium or tetraalkylphosphonium salt).[62] One practical limitations to the phase-transfer method, however, is that many of the catalysts used to promote the formation of stable emulsions which make the work-up very difficult. The attachment of phase-transfer catalysts (PTC) to insoluble polymer supports greatly eliminates the above limitation. This new type of heterogeneous catalysis was termed 'Triphase Catalysis' (Figure 2.1).[63]

Not only would catalyst recovery and product isolation be greatly simplified, but also, owing to the three-phase nature of the system, continuous flow methods could be employed making the technique particularly attractive for industrial applications.

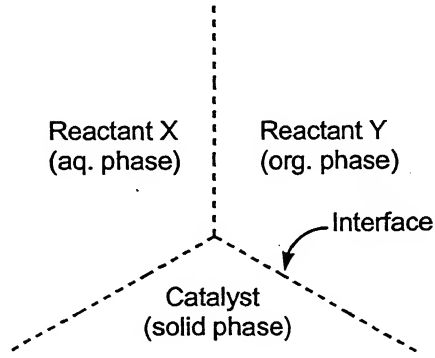
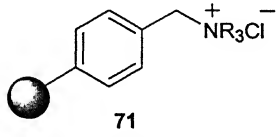


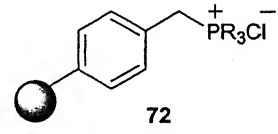
Figure 2.1

The underlying feature, which distinguishes triphase catalysis from other forms of heterogeneous catalysis, is that both the catalyst and each one of a pair of reactants are located in separate phases, and the reaction takes place at the interface of solid-aqueous and solid-organic phases. Generally, polymer anchored quaternary ammonium[63] **71** and phosphonium salts[64] **72** are used as catalysts in triphase catalyzed reactions (Figure 2.2).



71

R = alkyl

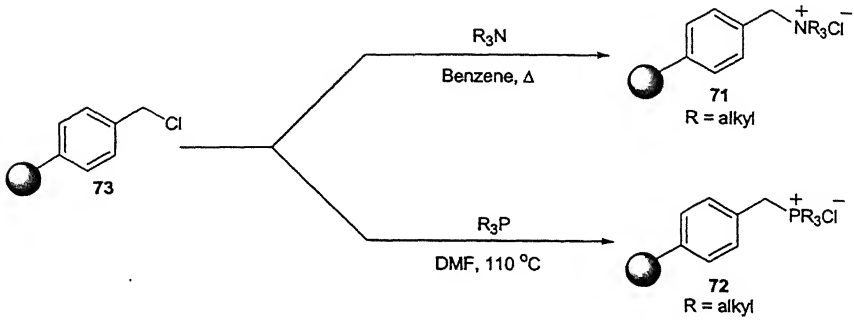


72

R = alkyl

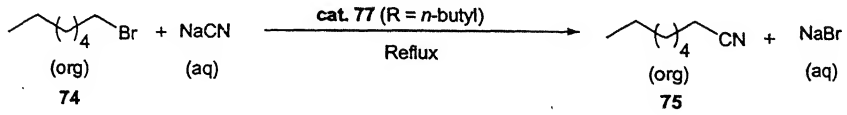
Figure 2.2

These catalysts **71** and **72** could be prepared by refluxing Merrifield resin **73** with trialkyl amine or trialkyl phosphine respectively in suitable solvents (Scheme 2.1). The extent of quaternization was determined by the chloride ion analysis using Volhard method.[65]



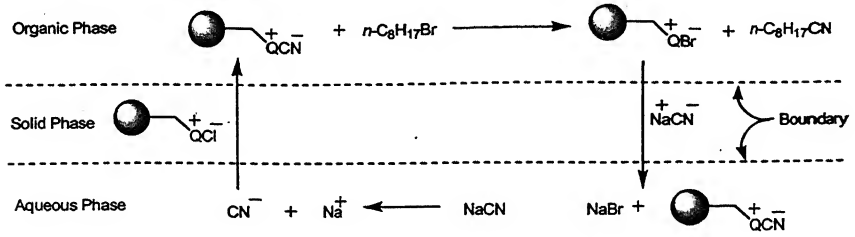
Scheme 2.1

The concept of triphase catalysis was first used in the displacement reactions of alkyl halides with NaCN.[63b,66] When 1-bromooctene **74** was treated with aqueous NaCN in the presence of catalytic amount of **71** (R = *n*-butyl), the product 1-cyanooctane **75** was obtained in 98% yield under reflux conditions (Scheme 2.2).



Scheme 2.2

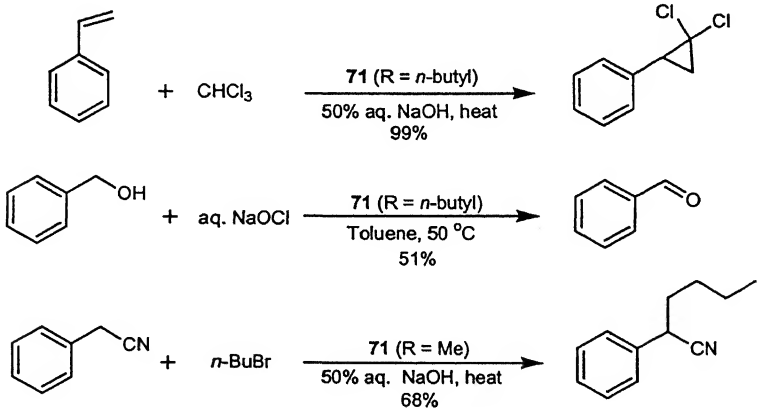
The mechanism of the above reaction may be represented as follows (Scheme 2.3).



Scheme 2.3

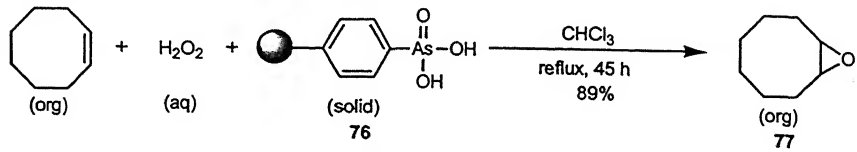
The mechanism of triphase catalysis is analogous to that shown for classical phase-transfer catalysis. As discussed above, the reaction occurs in the organic shell surrounding the catalytic site. Anions exchange at the interface of aqueous-organic phase, with the inorganic cation M^+ and the polymer-supported quaternary ammonium cation as counter ions in the aqueous and the organic phase.

Not only displacement reactions, the concept of triphase catalysis has been used in other transformations like cyclopropanation,[66] oxidation of alcohols[66] and C-alkylation of nitriles (Scheme 2.4).[67]



Scheme 2.4

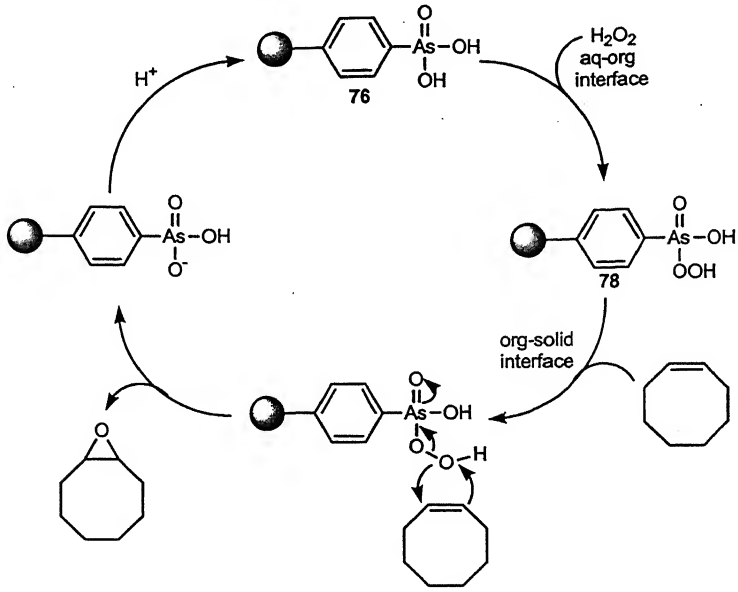
Jacobson and co-workers reported an efficient method for the epoxidation of olefins under triphasic conditions using arsonated polystyrenes as catalysts.[68] When a solution of cyclooctene in $CHCl_3$ was exposed to 30% aq. H_2O_2 in the presence of catalytic amounts of arsonated polystyrene **76** at reflux temperature, the epoxide **77** was obtained in 89% yield (Scheme 2.5).



Scheme 2.5

The mechanism of the above epoxidation reaction is represented in Scheme 2.6. The initial step is the formation of peroxyarsonic acid **78** by the reaction of arsonated polystyrene **76** with aqueous H_2O_2. The olefin then interacts the polymer anchored peroxyarsonic acid **78** at the organic-solid interface leading to the formation of the epoxide **77** and the catalyst **76**. Thus, the catalytic cycle is established.[68]

Since polymer supported reactions serve as a part of green chemistry, we became interested in that field. In this chapter, we wish to discuss our efforts toward the development of polymer supported phase transfer catalysts for the epoxidation of α,β-enones.

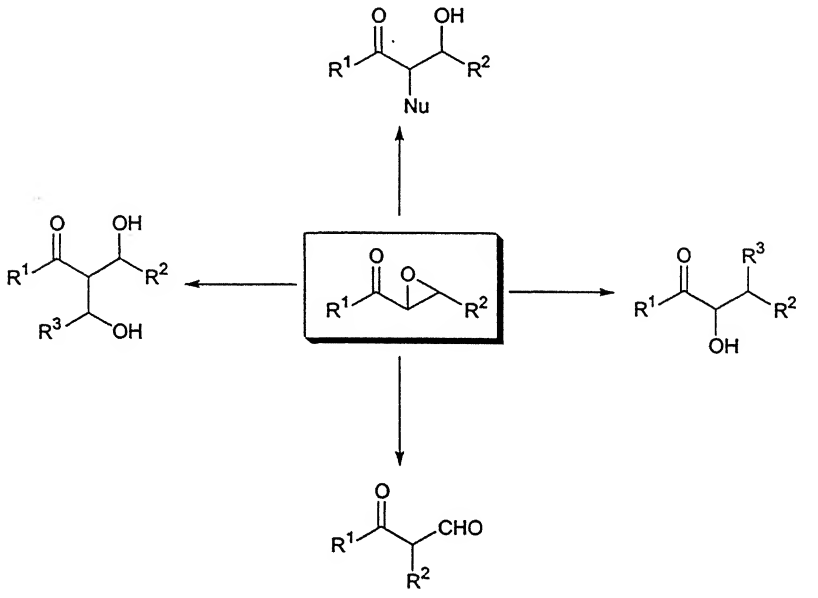


Scheme 2.6

2.1.1 Epoxidation of α,β-enones under triphasic conditions:

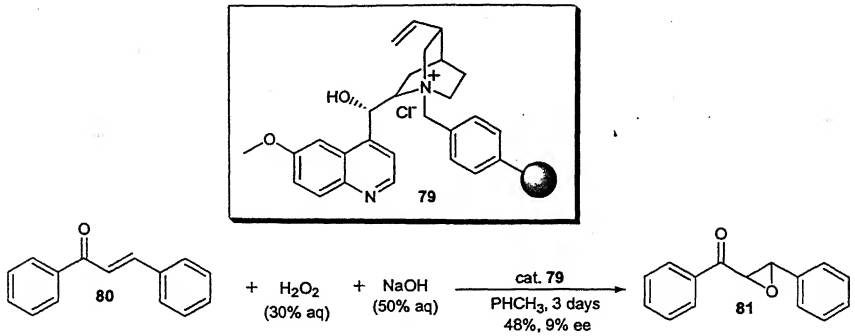
Epoxidation of α,β-enones (Weitz-Scheffer reaction) is one of the important transformations in organic synthesis because, the resulting epoxy ketones can be derivatized to a wide variety of useful compounds (Scheme 2.7). Generally, this transformation could be effected by using 30% aqueous H_2O_2 in water miscible solvents, such as acetone, under basic conditions.[69] The major disadvantage of this homogeneous method is that, in some cases, the epoxide formed undergoes over oxidation with H_2O_2 leading to the cleavage of the epoxide.[70] One of the alternative methods, to control the reaction, is to carry out the reaction in biphasic conditions using phase transfer catalysts.[71] But, the limitation associated with conventional PTCs is that

it forms a stable emulsion and makes the workup cumbersome. To overcome this limitation, polymer supported phase transfer catalysts (triphase catalysis) have been developed.



Scheme 2.7

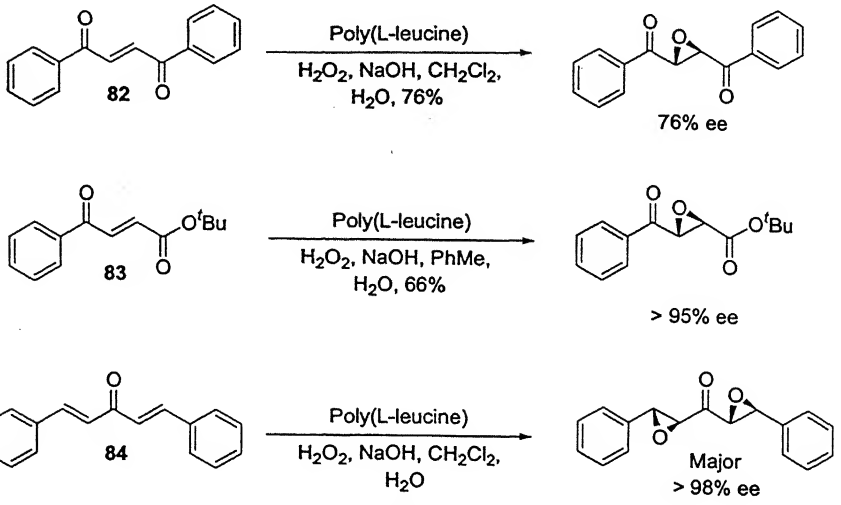
Kobayashi reported an asymmetric epoxidation of chalcones under triphase-catalyzed conditions using polystyrene anchored quininiumsalt **79** as a catalyst.[72] When chalcone **80** was treated with 30% aqueous H_2O_2 using catalytic amounts of **79**, the product chalcone epoxide **81** was obtained in 48% yield and 9% ee (Scheme 2.8).



Scheme 2.8

It was explained that the low yield and ee of **81** was due to the steric hindrance at the active quaternary ammonium center by the bulk polymeric backbone.

Juliá and Colonna found that polyalanine and polyleucine efficiently catalyzed the epoxidation of chalcones under triphase-catalyzed conditions.[73] Although both the yield and the ee of epoxides formed under these conditions are good, there are some disadvantages. First, the trans formation appeared to be limited to enones of the type (*E*)-$Ar^1CH{=}CHCOAr^2$, i.e., close relatives of chalcone.[73] Secondly, the catalyst forms a gel in the reaction mixture, which filters very slowly making difficult the recovery of the catalyst after completion of the reaction. Subsequently, it transpired that the three-phase reaction conditions could be used to epoxidize enediones **82**, enone esters **83** and dienones **84** (Scheme 2.9).


82
Poly(L-leucine)
H_2O_2, NaOH, CH_2Cl_2,
H_2O, 76%
76% ee
83
Poly(L-leucine)
H_2O_2, NaOH, PhMe,
H_2O, 66%
> 95% ee
84
Poly(L-leucine)
H_2O_2, NaOH, CH_2Cl_2,
H_2O
Major
> 98% ee

Scheme 2.9

2.2 Background:

While working on Green Chemistry,[1] as a part of our research, we became interested in polymer supported reactions, because polymer supported reagents or catalysts are potentially re-usable and create less waste than conventional materials and, as such, represent catalysts for green chemistry.

Epoxidation of α,β-enones is one of the important transformations in organic synthesis. This transformation could be effected by using 30% aqueous H_2O_2 in acetone under basic conditions.[69] As mentioned earlier, the major disadvantage of this homogeneous method is that, in some cases, the epoxide formed undergoes over oxidation with H_2O_2 leading to the cleavage of the epoxide.[70] One of the alternative methods, to control the reaction, is to carry out the reaction in biphasic conditions using phase transfer catalysts.[71] But, the limitation associated with conventional PTCs is that it forms a stable emulsion and makes the workup difficult. To overcome this limitation, polymer supported phase transfer catalysts (triphase catalysis) have been developed.[63]

In this chapter, the preparation and the use of two new polymer anchored phase transfer catalysts for the epoxidation of α,β-enones will be discussed.

Present Work:

Two new polymer anchored quaternary ammonium salt catalysts **85** and **86** (Figure 2.3) were prepared for the epoxidation of α,β-enones. These catalysts **85** and **86** were chosen because they resemble the conventional phase transfer catalysts **87** and **88** respectively.

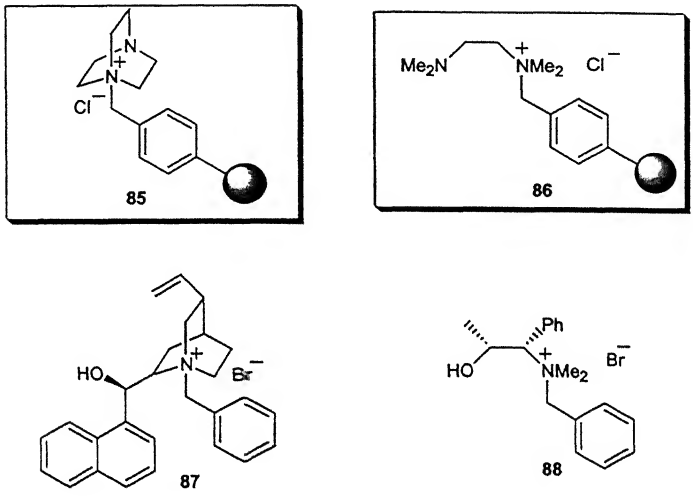
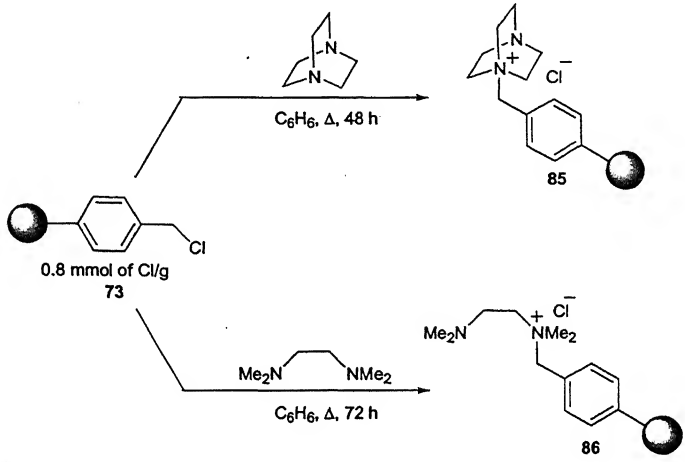


Figure 2.3

The catalysts **85** and **86** were prepared by treating Merrifield resin **75** (0.8 mmol of Cl/g of resin) with DABCO and TMEDA respectively in refluxing benzene (Scheme 2.10). The extent of quaternarization was determined by chloride ion analysis using Volhard procedure,[65] i.e., the polymer catalyst (**85** or **86**) was first titrated with a known excess of $AgNO_3$ solution and the excess $AgNO_3$ was back titrated with a standard NH_4SCN solution using ferric alum as an indicator. The end point was the appearance of red brown color. From

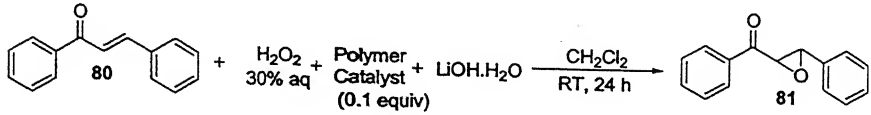
the amount of $AgNO_3$ reacted with polymer anchored quaternary ammonium chloride the amount of chloride ions present in the polymer was determined. Thus, The chloride ion content in polymer **85** was found to be 0.1 mmol/g. Similarly, the chloride ion content of polymer **86** was found to be 0.07 mmol/g.



Scheme 2.10

By using catalytic amounts of these two polymer catalysts (10 mol% of **85** and **86**), we carried out the epoxidation reaction of chalcone **80** under triphasic conditions using 30% aqueous H_2O_2 and $LiOH.H_2O$. In both the cases, the reaction was very clean and only one product was obtained. By using polymer catalyst **85**, the desired epoxide **81** was obtained in 95% yield after 24 h in CH_2Cl_2. The yield of epoxide **81** was a bit inferior (91%), when the polymer **86** was used as a catalyst (Scheme 2.11). Since, polymer **85** gave better result than **86**, we used polymer **85** for further investigation. Using this catalys

diethyl ether (98% yield, 20 h) was superior to CH_2Cl_2 (94% yield, 20 h), $CHCl_3$ (50% yield, 20 h) and benzene (40% yield, 20 h).



Catalysts	Yield
85	95%
86	91%

Scheme 2.11

The best result was obtained when 0.5 mmol of chalcone **80** was treated with 1 ml of 30% aqueous H_2O_2 and 2.5 mmol of $LiOH.H_2O$ in the presence of 0.05 mmol of the catalyst in diethyl ether at RT. By using the above standard conditions a variety of α,β-enones could be transformed to their corresponding epoxides and the results are summarized in Figure 2.4.[74]

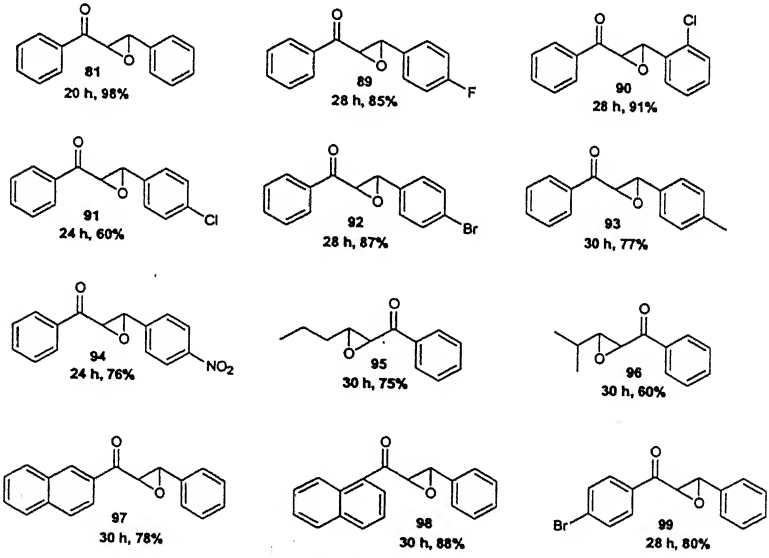
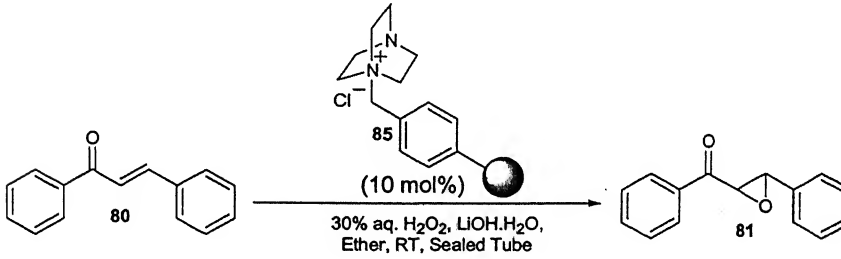


Figure 2.4

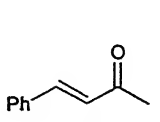
In almost all the cases, the reaction proceeded very smoothly and the corresponding epoxide was obtained in high yield. In the absence of polymer catalyst, there was no epoxidation reaction even after 2 days at RT. An interesting feature of this reaction is that the catalyst could be recovered after the reaction and reused without losing its activity. The recovered catalyst in the first run was dried in air for 2 days and was used for the second run. The catalyst recovered from the second run was dried and used for third run. The most notable observation was that the reuse of the same catalyst did not diminish the catalytic activity in the reaction (Scheme 2.12).



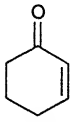
Run	Time	Yield
1	20 h	98%
2	24 h	92%
3	30 h	89%

Scheme 2.12

The only drawback of the reaction was that the reaction failed in cases where alkyl group was attached to the ketonic group of the enone system. For example, substrates like **100** and **101** did not undergo epoxidation reaction under triphasic conditions using polymer catalyst **90** (Figure 2.5). This could be due to decrease of reactivity of β-C of enone system towards peroxide ion.



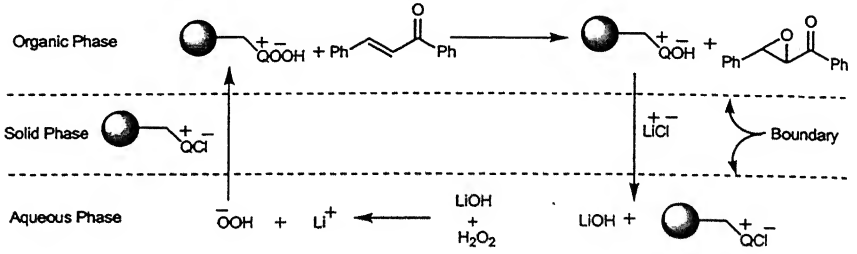
100



101

Figure 2.5

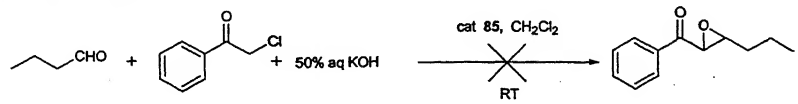
The mechanism of epoxidation reaction under triphase catalysis is analogous to that of classical phase-transfer catalysis. The peroxide anion is transported from the aqueous phase to the organic phase *via* polymer anchored phase transfer catalyst (solid phase). The epoxidation reaction takes place at the solid-organic interface (Scheme 2.13).



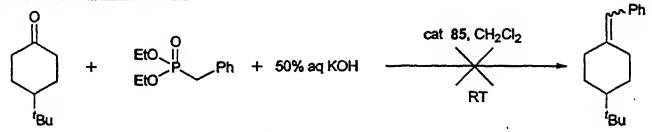
Scheme 2.13

In order to show the applicability in organic synthesis, the catalyst **85** was applied for other transformation like Darzen reaction, Horner-Emmons reaction, C-alkylation of active methylene compounds, Nitro aldol reaction and hydrophosphonylation of aldehydes. But, unfortunately, none of the reaction gave the desired product under triphasic conditions using the polymer catalyst **85** (Scheme 2.14).

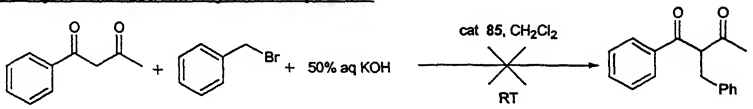
Darzen Reaction:



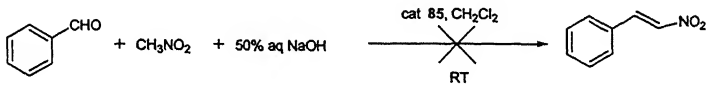
Horner-Emmons reaction:



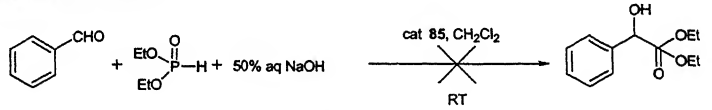
C-alkylation of activ methylene compounds:



Nitro aldol reaction:



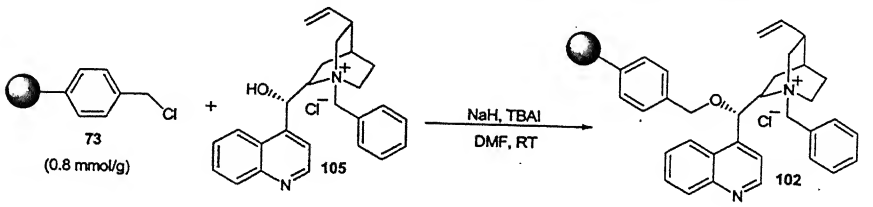
Hydrophosphonylation:



Scheme 2.14

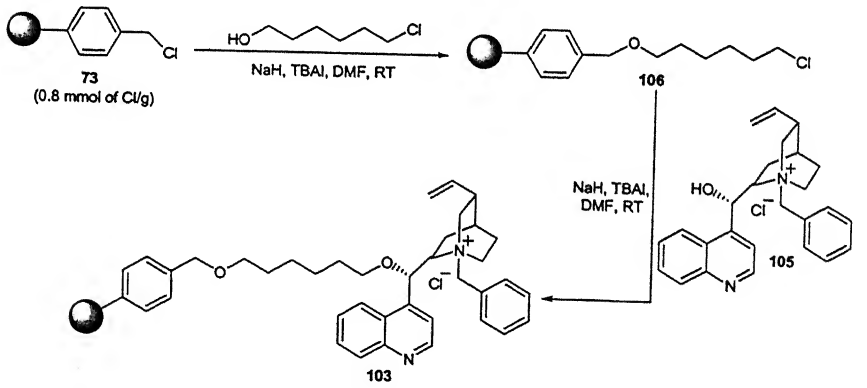
Since, the epoxidation of α,β-enones is very efficient under triphasic conditions by using the polymer catalyst **85**, we shifted our attention towards asymmetric version of the reaction. We prepared three chiral polymer anchored phase transfer catalysts **102**, **103** and **104** for asymmetric epoxidation reaction. The polymer catalyst **102** was prepared by treating Merrifield resin with commercially available cinchona based phase transfer catalyst **105** in the presence of NaH and

TBAI (Scheme 2.15). By using Volhard method, the Cl ion content in the polymer catalyst **102** was found to be 0.21 mmol/g of resin.



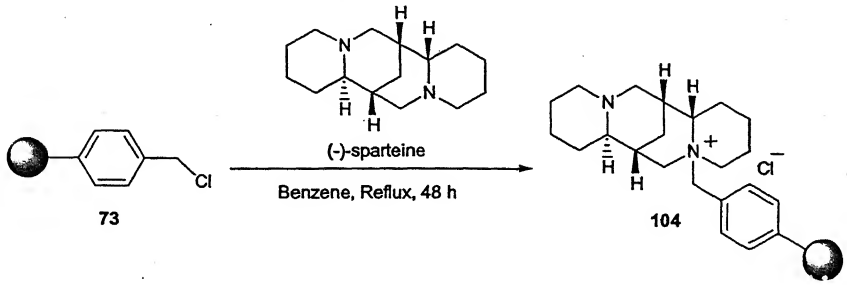
Scheme 2.15

The polymer catalyst **103** was prepared as shown in the Scheme 2.16. First, Merrifield resin was treated with 6-chlorohexanol under NaH conditions to get the polymer anchored ether **106**, which was filtered and dried. The polymer **106** on treatment with **105** in the presence of NaH, TBAI gave the polymer **103**. The chloride ion content of **102** was found to be 0.056 mmol of Cl/g of resin.



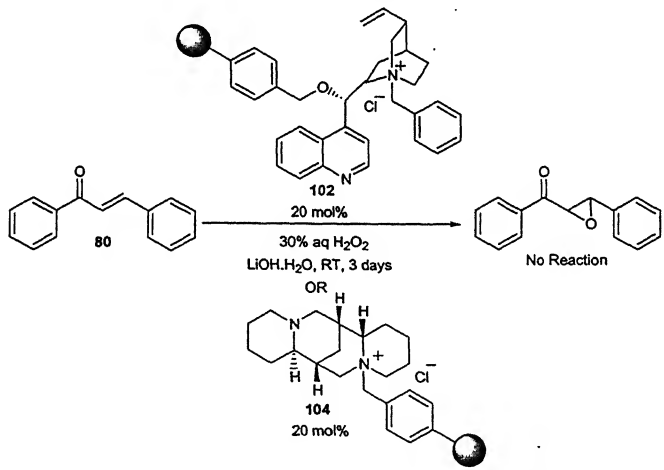
Scheme 2.16

The polymer **104** was prepared by treating Merrifield resin with (-)-spartiene in refluxing benzene (Scheme 2.17). The chloride ion content, in this case, was found to be 0.048 mmol of Cl/g of resin.



Scheme 2.17

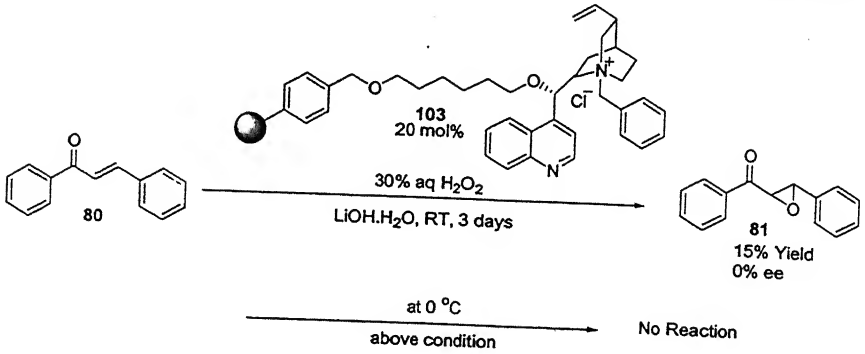
Unfortunately, chalcone on reaction with 30% aqueous H_2O_2 and $LiOH.H_2O$ in the presence of 20 mol% of **102**, showed no epoxide formation at RT even after 3 days. Also, no epoxide formation was observed when 20 mol% of **104** was used (Scheme 2.18).



Scheme 2.18

By using the catalyst **103** only the racemic epoxide **81** was obtained in 15% yield after 3 days at RT (Scheme 2.19). When we carried out the same reaction at 0 °C, the reaction was sluggish and no

epoxide formation was observed. Since there was no chiral induction observed in all the cases, we temporarily stopped our work at this stage.



Scheme 2.19

In conclusion, we have prepared two new polymer anchored quaternary ammonium salt catalysts for the epoxidation of α,β-enones. A variety of chalcone derivatives could be transformed to their corresponding epoxides under triphasic conditions. The polymer catalyst used was recycled and reused several times without losing its catalytic activity. However, polymer anchored chiral phase transfer catalysts failed to provide asymmetric induction.

2.4. Experimental Section.

The common materials and methods have already been given in the experimental section of the chapter 2, Part A. Merrifield resin (0.8 mmol of Cl/g) and (1.26 mmol of Cl/g) were obtained from Fluka. DABCO, TMEDA, *N*-benzyl cinchoninium chloride and (-)-spartiene sulfate were obtained from Fluka and used as received.

Preparation of the polymer bound quaternary ammonium salt 85. The Merrifield resin [0.8 mmol of Cl/gram of resin] (1.0 g, 0.8 mmol) was added to a solution of DABCO (180 mg, 1.6 mmol) in *anhydrous* benzene (20 mL) and the resulting suspension was heated at 80 °C for 2 days in a sealed tube. It was filtered, washed several times with benzene and ether. It was dried under vacuum at 60 °C for 3 h. Yield 1.06 g. Elemental Analysis: C, 81.69; H, 7.47; N, 1.85.

Determination of chloride ion content of polymer 85 by Volhard method.[65b] A standard solution of $AgNO_3$ (0.05 *N*, 10 mL) was added to a suspension of polymer bound catalyst **85** (200 mg) in dilute HNO_3 solution (2 mL). After five minutes, toluene (2 mL) was added to it and the resulting suspension was stirred well for further five minutes. This suspension was titrated against a standard solution of NH_4SCN (0.05 *N*) using ferric alum as an indicator. The end point was the appearance of red-brown color due to the formation of $Fe(SCN)_3$.

Calculations:

Volume of standard $AgNO_3$ solution = 10 mL

Volume of standard NH_4SCN solution consumed = 9.6 mL

Therefore, volume of standard $AgNO_3$ solution consumed = 0.4 mL

10 mL of $AgNO_3$ solution contains 85 mg of $AgNO_3$

Therefore, 0.4 mL of $AgNO_3$ solution will contain 3.4 mg of $AgNO_3$.

169.87 mg of $AgNO_3$ replaces 36.5 mg of chloride ions.

Therefore, 3.4 mg of $AgNO_3$ will replace 0.73 mg of chloride ions, which means 0.73 mg of chloride ions are present in 200 mg of the polymer bound catalyst **85**.

Therefore, 1 g of polymer will contain 3.653 mg of chloride ions. It means 1 g of polymer will contain 3.653/36.5 mmol of chloride ions. Thus, the chloride ion content in the polymer catalyst **85** was found to be 0.1 mmol per gram of resin.

Preparation of polymer bound quaternary ammonium salt 86. The Merrifield resin [0.8 mmol of Cl/gram of resin] (1.0 g, 0.8 mmol) was added to a solution of TMEDA (240 μL, 1.6 mmol) in *anhydrous* benzene (20 mL) and the resulting suspension was heated at 80 °C for 3 days in a sealed tube. It was filtered, washed several times with benzene and ether. It was dried under vacuum at 60 °C for 3 h. Yield 1.03 g. Elemental analysis: C, 83.82; H, 7.59; N, 1.44. The chloride ion analysis was performed as mentioned above and was found to be 0.07 mmol of chlorine per gram of resin.

General procedure for the preparation of chalcones. Few drops of 50% aqueous NaOH solution was added to a solution of an aldehyde (1.1 mmol) and an aryl methyl ketone (1 mmol) in ethanol (4 mL) at 0 °C. The reaction mixture was warmed to rt and stirred for 24 h. It was kept in the refrigerator for overnight. The solid formed was filtered and washed with cold ethanol and recrystallized from ethanol.

General procedure for epoxidation of enones. An enone (0.5 mmol) and 30% aqueous H_2O_2 (1 mL) were added to a suspension of polymer catalyst (**85** or **86**, 0.05 mmol) in ether (4 mL) and stirred for 10 minutes. $LiOH.H_2O$ (2.5 mmol) was then added and the reaction mixture was further stirred at rt till the starting material was consumed. It was filtered, washed with ether and 1*N* HCl. The organic phase was separated and the aqueous phase was extracted with ether. The combined organic layer was washed with brine, dried over *anhydrous* Na_2SO_4 and concentrated. The crude material was purified by silica gel column chromatography to get pure epoxide. The recovered catalyst was dried in air for 2 days and was also reused for the reaction.

Phenyl-(3-phenyl-oxiranyl)-methanone 81.[71b] Yield 98%; White solid; mp 77-80 °C; R_f 0.60 (5% EtOAc in petroleum ether); FT IR (KBr) 1678 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.07 (d, J = 2.0 Hz, 1H), 4.29 (d, J = 1.9 Hz, 1H), 7.35-7.43 (m, 5H), 7.49 (t, J = 7.8 Hz, 2H), 7.59-7.64 (m, 1H), 7.99-8.05 (m, 2H).

[3-(4-Fluoro-phenyl)-oxiranyl]-phenyl-methanone 89. Yield 85%; White solid; mp 87-89 °C; R_f 0.45 (5% EtOAc in petroleum ether); FT IR (KBr) 1686 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.99 (d, J = 1.7 Hz, 1H), 4.19 (d, J = 1.7 Hz, 1H), 6.99-7.05 (m, 2H), 7.25-7.29 (m, 2H), 7.43 (t, J = 8.0 Hz), 7.53-7.58 (m, 1H), 7.94 (dd, J = 8.6, 1.2 Hz, 2H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 58.79, 60.94, 115.84 (d, $^2J_{CF}$ = 22.2 Hz), 127.51, 128.33, 128.63, 128.89, 134.08, 135.35, 163.15 (d, $^1J_{CF}$ = 246.8 Hz, one bond F coupling), 192.89.

[3-(2-Chloro-phenyl)-oxiranyl]-phenyl-methanone 90.[71a] Yield 91%; Pale yellow solid; mp 69-71 °C; R_f 0.50 (10% EtOAc in petroleum ether); FT IR (KBr) 1694 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.17 (d, J = 2.0 Hz, 1H), 4.40 (d, J = 1.6 Hz, 1H), 7.30-7.34 (m, 2H), 7.38-7.41 (m, 2H), 7.48-7.52 (m, 2H), 7.61-7.65 (m, 1H), 8.05 (d, J = 7.3 Hz, 2H).

[3-(4-Chloro-phenyl)-oxiranyl]-phenyl-methanone 91.[76] Yield 60%; White solid; mp 79-82 °C; R_f 0.30 (2% EtOAc in petroleum ether); FT IR (KBr) 1680 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.06 (d, J = 1.7 Hz, 1H), 4.25 (d, J = 1.9 Hz, 1H), 7.30-7.32 (m, 2H), 7.36-7.39 (m, 2H), 7.48-7.52 (m, 2H), 7.61-7.65 (m, 1H), 8.01 (d, J = 7.1 Hz, 2H).

[3-(4-Bromo-phenyl)-oxiranyl]-phenyl-methanone 92. Yield 87%; White solid; mp 89-91 °C; R_f 0.32 (5% EtOAc in petroleum ether); FT IR (KBr) 1658 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.05 (d, J = 1.6 Hz, 1H), 4.24 (d, J = 2.0 Hz, 1H), 7.25 (d, J = 8.6 Hz, 2H), 7.48-7.64 (m, 5H), 7.99 (m,2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 58.76, 60.85, 122.18, 127.35, 128.35, 128.94, 131.97, 134.13, 134.55, 135.33, 192.69.

Phenyl-(3-*p*-tolyl-oxiranyl)-methanone 93.[76] Yield 77%; Pale yellow solid; mp 80-83 °C; R_f 0.35 (5% EtOAc in petroleum ether); FT IR (KBr) 1679 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.36 (s, 3H), 4.02 (d, J = 1.4 Hz, 1H), 4.28 (d, J = 1.7 Hz, 1H), 7.19-7.26 (m, 4H), 7.44-7.48 (m, 2H), 7.58-7.61 (m, 1H), 7.99 (d, J = 8.3 Hz, 2H).

[3-(4-Nitro-phenyl)-oxiranyl]-phenyl-methanone 94. Yield 76%; White solid; mp 134-136 °C; R_f 0.40 (20% EtOAc in petroleum ether); FT IR (KBr) 1677, 1515 cm^{-1} (asymmetric NO_2 stretch), 1345 cm^{-1}

(symmetric NO_2 stretch); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.21 (d, J = 1.7 Hz, 1H), 4.29 (d, J = 1.7 Hz, 1H), 7.43-7.67 (m, 5H), 8.00-8.02 (m, 2H), 8.24-8.28 (m, 2H).

Phenyl-(3-propyl-oxiranyl)-methanone 95.[77] Yield 75%; Viscous paste; R_f 0.50 (10 % EtOAc in petroleum ether); FT IR (film) 1690 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.13 (t, J = 7.2 Hz, 3H), 1.36-1.44 (m, 2H), 1.61-1.86 (m, 2H), 2.89 (dd, J = 6.8, 2.2 Hz, 1H), 4.02 (d, J = 2.0, 1H), 7.40-7.44 (m, 2H), 7.52-7.56 (m, 1H), 7.93-7.95 (m, 2H).

(3-Isopropyl-oxiranyl)-phenyl-methanone 96.[77] Yield 60%; Colorless oil; R_f 0.55 (5% EtOAc in petroleum ether); FT IR (film) 1694 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.04 (d, J = 7.2 Hz, 3H), 1.13 (d, J = 7.2 Hz, 3H), 1.69-1.85 (m, 1H), 3.01 (dd, J = 6.8, 2.0 Hz, 1H), 4.02 (d, J = 2.0 Hz, 1H), 7.41-7.53 (m, 2H), 7.59-7.69 (m, 1H), 7.98-8.10 (m, 2H).

Naphthalen-2-yl-(3-phenyl-oxiranyl)-methanone 97.[76] Yield 78%; White solid; mp 124-127 °C; R_f 0.45 (10% EtOAc in petroleum ether); FT IR (KBr) 1680 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.14 (d, J = 1.7 Hz, 1H), 4.42 (d, J = 2.0 Hz, 1H), 7.37-7.40 (m, 5H), 7.51-7.62 (m, 2H), 7.84-7.92 (m, 3H), 8.03 (dd, J = 8.5, 1.7 Hz, 1H), 8.53 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 59.46, 60.99, 123.63, 125.84, 127.08, 127.86, 128.56, 128.86, 129.05, 129.70, 130.42, 130.45, 132.36, 132.81, 135.54, 135.89, 192.95.

Naphthalen-1-yl-(3-phenyl-oxiranyl)-methanone 98.[71b] Yield 88%; White solid; mp 76-79 °C; R_f 0.50 (10% EtOAc in petroleum ether); FT IR (KBr) 1679 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.01 (d, J = 1.7

Hz, 1H), 4.11 (d, J = 2.0 Hz, 1H), 7.23-7.28 (m, 4H), 7.31-7.48 (m, 3H), 7.71-7.76 (m, 2H), 7.81 (d, J = 7.3 Hz, 1H), 7.88 (d, J = 8.5 Hz, 2H), 8.56 (d, J = 8.5 Hz, 1H).

(4-Bromo-phenyl)-(3-phenyl-oxiranyl)-methanone 99.[71b] Yield 80%; White solid; mp 92-94 °C; R_f 0.74 (5% EtOAc in petroleum ether); FT IR (KBr) 1678 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.07 (d, J = 2.0 Hz, 1H), 4.22 (d, J = 2.0 Hz, 1H), 7.34-7.43 (m, 5H), 7.61-7.66 (m, 2H), 7.86-7.90 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 59.38, 61.05, 125.6, 128.80, 129.16, 129.39, 129.85, 132.23, 134.07, 135.21, 192.27.

Preparation of polymer bound quaternary ammonium salt 102. A solution of *N*-benzyl cinchoninium chloride (198 mg, 0.44 mmol) in *anhydrous* DMF (5 mL) was added drop-wise to a suspension of NaH [60% suspension in mineral oil] (32 mg, 0.08 mmol) and TBAI (15 mg, 0.04 mmol) in *anhydrous* DMF (15 mL) at 0 °C. After being stirred for 10 minutes, the reaction mixture was warmed to rt and Merrifield resin [0.8 mmol of Cl/gram of resin] (500 mg, 0.4 mmol) was added portion wise to it. The reaction mixture was further stirred for 24 h at rt. It was quenched with *aqueous* NH_4Cl solution, then filtered and washed with DMF, water, DMF-water mixture, THF and finally with ether. The polymer thus obtained **102** was dried under vacuum at 60 °C for 3 h. Yield 509 mg. The chloride ion content was found to be 0.21 mmol per gram of resin. Elemental analysis: C, 82.82; H, 7.78; N, 2.44.

Preparation of polymer bound quaternary ammonium salt 103. This involved 2 steps.

*Preparation of **106**:*

6-Chlorohexanol (258 mg, 1.89 mmol) was added drop-wise to a suspension of NaH [60% suspension in mineral oil] (100 mg, 2.52 mmol) and TBAI (47 mg, 0.13 mmol) in *anhydrous* DMF (25 mL) at 0°C. After being stirred for 15 minutes, the reaction mixture was warmed to rt and Merrifield resin [1.26 mmol of Cl/g of resin] (1g, 1.26 mmol) was added portion wise to it. The resulting heterogeneous suspension was stirred at rt for additional 24 h. It was quenched with aqueous NH_4Cl solution and filtered. The polymer **106** was then washed with DMF, water, DMF-water mixture, THF and finally with ether. The polymer was then dried under vacuum at 60 °C for 3 h. Yield 1.13 g. it was used directly for the next step.

*Preparation of **103**:*

A solution of *N*-benzyl cinchoninium chloride (636 mg, 1.51 mmol) in *anhydrous* DMF (5 mL) was added drop-wise to a suspension of NaH [60% suspension in mineral oil] (151 mg, 3.78 mmol) and TBAI (47 mg, 0.126 mmol) in *anhydrous* DMF (15 mL) at 0 °C. After being stirred for 10 minutes, the reaction mixture was warmed to rt and resin **106** [we assumed it contains 1.26 mmol of Cl/g of resin] (1.13 g, 1.26 mmol) was added portion wise to it. The reaction mixture was further stirred for 24 h at rt. It was quenched with *aqueous* NH_4Cl solution, then filtered and washed with DMF, water, DMF-water mixture, THF and finally with ether. The polymer was then dried under vacuum at 60 °C for 3 h. Yield 1.15 g. The chloride ion content was found to be

0.056 mmol per gram of resin. Elemental analysis: C, 84.82; H, 7.62; N, 1.01.

Preparation of polymer bound quaternary ammonium salt 104. The Merrifield resin [0.8 mmol of Cl/gram of reasin] (1 g, 0.8 mmol) was added to a solution of (-)-sparteine (380 mg, 1.6 mmol) in *anhydrous* benzene (20 mL) and the resulting suspension was heated at 80 °C for 3 days in a sealed tube. It was filtered, washed several times with benzene and ether. It was dried under vacuum at 60 °C for 3 h. Yield 1.09 g. The chloride ion analysis was performed as mentioned above and was found to be 0.048 mmol of chlorine per gram of resin. Elemental analysis: C, 81.62; H, 8.06; N, 1.02.

References:

1. a) Anastas, P. T.; Warner, J. C. *Green Chemistry: Theory and Practice*; Oxford Science Publications, New York, 1998. b) Anastas, P. T.; Williamson, T. *Green Chemistry, Frontiers in Benign Chemical Synthesis and Processes*; Oxford Science Publications, New York, 1998. c) For a review, see: Anastas, P. T.; Kirchhoff, M. M. *Acc. Chem. Res.* **2002**, *35*, 686, and references cited therein. d) For a review on atom economy, see: Trost, B. M. *Acc. Chem. Res.* **2002**, *35*, 695.
2. a) Welton. T. *Chem. Rev.* **1999**, *99*, 2701. b) Holbrey, J. D.; Seddon, K. R. *J. Chem. Soc., Dalton Trans.* **1999**, 2133. c) Scott, J. L.; MacFarlane, D. R.; Raston, C. L.; Teoh, M. *Green Chem.* **2000**, *2*, 123.
3. a) Leitner, W. *Acc. Chem. Res.* **2002**, *35*, 746. b) Oakes, R. S.; Heppenstall, T. J.; Shezad, N.; Clifford, A. A.; Rayner, C. M. *Chem. Commun.* **1999**, 1459. c) Shezad, N.; Clifford, A. A.; Rayner, C. M. *Tetrahedron Lett.* **2001**, *42*, 323. d) Darr, J. A.; Poliakoff, M. *Chem. Rev.* **1999**, *99*, 495.
4. a) Li, C. -H; Chen, T. *Organic Reactions in Aqueous Media*; Wiley Interscience, New York, 1997. b) Li, C. -H.; Zhang, W. –C. *J. Am. Chem. Soc.* **1998**, *120*, 9102. c) Strauss, C. R. *Aust. J. Chem.* **1999**, *52*, 83, and references therein.
5. For reviews on microwave assisted organic synthesis, see: a) Larhed, M.; Moberg, C.; Hallberg, A. *Acc. Chem. Res.* **2002**,

35, 717. b) Lidström, P.; Tierney, J.; Wathey, B.; Westman, J. *Tetrahedron* **2001**, *57*, 9225.

6. Roberts, B. A.; Cave, G. W. V.; Raston, C. L.; Scott, J. L. *Green Chem.* **2001**, 280.
7. For reviews on solvent free organic synthesis, see: a) Cave, G. W. V.; Raston, C. L.; Scott, J. L. *Chem. Commun.* **2001**, 2159. b) Toda, F.; Tanaka, K. *Chem. Rev.* **2000**, *100*, 1025. c) Toda, F. *Acc. Chem. Res.* **1995**, *28*, 480. d) Toda, F. *Synlett.* **1993**, 303.
8. a) Cave, G. W. V.; Hardie, M. J.; Roberts, B. A.; Raston, C. L. *Eur. J. Org. Chem.* **2001**, 3227. b) Rothenberg, G.; Downie, A. P.; Raston, C. L.; Scott, J. L. *J. Am. Chem. Soc.* **2001**, *123*, 8701. c) Orita, A.; Jiang, L.; Nakano, T.; Ma, N.; Otera, J. *Chem. Commun.* **2002**, 1362.
9. a) Clark, J. H. *Catalysis of Organic Reactions by Supported Inorganic Reagents*; VCH Publisher: New York, 1994. b) Balogh, M.; Laszlo, P. *Organic Chemistry Using Clays*; Springer-Verlag: Berlin, 1993. c) Clark, J. H.; Kybett, A. P.; Macquarrie, D. J. *Supported reagents Preparation, Analysis and Applications*; VCH: New York, 1992. d) Clark, J. H.; Macquarrie, D. J. *Chem. Commun.* **1998**, 853. e) Posner, G. H. *Angew. Chem. Int. Ed. Engl.* **1978**, *17*, 487.
10. a) Varma, R. S. *Green Chem.* **1999**, *1*, 43. b) Loupy, A.; Petit, A.; Hamelin, J.; Texier-Boullet, F.; Jacqualt, P.; Mathé, D.

Synthesis **1998**, 1213. c) Paul, S.; Gupta, V.; Gupta, R.; Loupy, A. *Tetrahedron Lett.* **2003**, *44*, 439, and references therein.

11. a) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 2nd Ed; Wiley: New York, 1991; pp. 188-191. b) Kocienski, P. J. *Protecting Groups*; Thieme: Stuttgart, 1994; pp. 156-170.
12. a) Corey, E. J.; Seebach, D. *J. Org. Chem.* **1966**, *31*, 4097. b) Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 239. c) Page, B.; van Niel, M. B.; Prodger, J. *Tetrahedron* **1989**, *45*, 7643.
13. Pettit, G. R.; van Tamelan, E. E. *Org. React.* **1962**, *12*, 356.
14. For a review, see: a) "*Comprehensive Organic Synthesis*," Eds. Trost, B. M. and Flemming, I., Pergamon, Oxford, 1991, Vol. 1, Part 2.4, p 541.
15. Corey, E. J.; Shimoji, K. *Tetrahedron Lett.* **1983**, *24*, 169.
16. Fieser, L. F. *J. Am. Chem. Soc.* **1954**, *76*, 1945.
17. Ong, B. S. *Tetrahedron Lett.* **1980**, *21*, 4225.
18. Kumar, V.; Dev, S. *Tetrahedron Lett.* **1983**, *24*, 1289.
19. Garlaschelli, L.; Vidari, G. *Tetrahedron Lett*, **1990**, *31*, 5815.
20. Firouzabadi, H.; Iranpoor, N.; Karimi, B. *Synthesis* **1999**, 58.
21. Mandal, P. K.; Roy, S. C. *Tetrahedron* **1995**, *51*, 7823.
22. Yadav, J. S.; Reddy, B. V. S.; Pandey, S. K. *Synlett* **2001**, 238.
23. Muthusamy, S.; Babu, S. A.; Gunanathan, C. *Tetrahedron Lett.* **2001**, *42*, 359.
24. Kamal, A.; Chouhan, G. *Tetrahedron Lett.* **2002**, *43*, 1347.

25. Janeshwara, G. K.; Barhate, N. B.; Sudalai, A.; Deshpande, V. H.; Wakhearar, R. D.; Gajare, A. S.; Shingare, M. S.; Sukumar, R. *J. Chem. Soc., Perkin Trans. 1* **1998**, 965, and references therein.

26. Kamal, K.; Chouhan, G.; Ahmed, K. *Tetrahedron Lett.* **2002**, *43*, 6947.

27. Clark, J. H. *Acc. Chem. Res.* **2002**, *35*, 791.

28. Kumar, P.; Reddy, R. S.; Singh, A. P.; Pandey, B. *Tetrahedron Lett.* **1992**, *33*, 825.

29. Ponde, D.; Borate, H. B.; Sudalai, A.; Ravindranathan, T.; Deshpande, V. H. *Tetrahedron Lett.* **1996**, *37*, 4605.

30. Patney, H. K. *Tetrahedron Lett.* **1991**, *32*, 2259.

31. Chandrasekhar, S.; Takhi, M.; Reddy, Y. R.; Mohapatra, S.; Rao, C. R.; Reddy, K. V. *Tetrahedron* **1997**, *53*, 14997.

32. Patney, H. K.; Margan, S. *Tetrahedron Lett.* **1996**, *37*, 4621.

33. Patney, H. K. *Tetrahedron Lett.* **1994**, *35*, 5717.

34. Ham, G. E. *J. Org. Chem.* **1964**, *29*, 3052.

35. For reviws, see: a) Sweeny, J. B. *Chem. Soc. Rev.* **2002**, *31*, 247. b) Davis, F. A. *Synthesis* **2000**, 1347. c) Tanner, D. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 599.

36. a) Iwakura, Y.; Nebeya, A. *J. Org. Chem.* **1960**, *25*, 1118. b) Kashelikar, D. V.; Fanta, P. E. *J. Org. Chem.* **1961**, *26*, 1841. c) Clapp, L. B. *J. Am. Chem. Soc.* **1948**, *70*, 184. d) Coleman, G. H.; Callen, J. E. *J. Am. Chem. Soc.* **1946**, *68*, 2006. e) Ghiraedelli, R,; Lucas, H. *J. Am. Chem. Soc.* **1957**, *79*, 734.

37. a) Meguro, M.; Asao, N.; Yamamoto, Y. *Tetrahedron Lett.* **1994**, *35*, 7395. b) Meguro, M.; Yamamoto, Y. *Heterocycles* **1996**, *43*, 2473.

38. Christoffers, J.; Schulze, Y.; Pickardt, J. *Tetrahedron* **2001**, *57*, 1765.

39. Yadav, J. S.; Reddy, B. V. S.; Jyothirmai, B.; Murty, M. S. R. *Synlett* **2002**, 53.

40. Yadav, J. S.; Reddy, B. V. S.; Parimala, G. *Synlett* **2002**, 1143.

41. Paul, B. J.; Hobbs, E.; Buccino, P.; Hudlicky, T. *Tetrahedron Lett.* **2001**, *42*, 6433.

42. Sekar, G.; Singh, V. K. *J. Org. Chem.* **1999**, *64*, 2537.

43. Chandrasekhar, M.; Sekar, G.; Singh, V. K. *Tetrahedron Lett.* **2000**, *41*, 10079.

44. Clark, J. H. *Acc. Chem. Res.* **2002**, *35*, 791.

45. For a review on $Cu(OTf)_2$ in organic synthesis, see: Hertweck, C. *J. Prakt. Chem.* **2000**, 342.

46. Sekar, G.; Singh, V. K. *J. Org. Chem.* **1999**, *64*, 287.

47. Saravanan, P.; Anand, R. V.; Singh, V. K. *Tetrahedron Lett.* **1998**, *39*, 3823.

48. Singh, R. P.; Kamble, R. M.; Chandra, K. L.; Saravanan, P.; Singh, V. K. *Tetrahedron* **2001**, *57*, 241.

49. a) Saravanan, P.; Singh, V. K. *Tetrahedron Lett*, **1999**, *40*, 2611. b) Chandra, K. L.; Saravanan, P.; Singh, R. K.; Singh, V. K. *Tetrahedron* **2002**, *58*, 1369.

50. Kamble, R. M.; Singh, V. K. *Tetrahedron Lett.* **2001**, *42*, 7525.

51. Chandra, K. L.; Saravanan, P.; Singh, V. K. *Tetrahedron Lett.*, **2001**, *42*, 5309.

52. Anand, R. V.; Saravanan, P.; Singh, V. K. *Synlett* **1999**, 415.

53. Sekar, G.; Singh, V. K. *J. Org. Chem.* **1999**, *64*, 2537.

54. a) Prasad, B. A. B.; Sekar, G.; Singh, V. K. *Tetrahedron Lett*, **2000**, *41*, 4677. b) Prasad, B. A. B.; Sanghi, R.; Singh, V. K. *Tetrahedron* **2002**, *58*, 7355.

55. For some examples using SiO_2 as an acid catalyst, see: a) Kotsuki, H.; Shimanouchi, T.; Ohshima, R.; Fujiwara, S. *Tetrahedron* **1998**, *54*, 2709. b) Kova, F. *Tetrahedron Lett.* **2001**, *42*, 5313. c) Kropp, P. J.; Breton, G. W.; Craig, S. L.; Crawford, S. D.; Durland, Jr., W. F.; Jones, III, J. E.; Raleigh, J. S. *J. Org. Chem.* **1995**, *60*, 4146. d) Pérez, J. M.; López, A. P.; Alonso, M. A.; Avendano, C.; Menéndez, J. C. *Tetrahedron Lett*, **1996**, *37*, 6955. e) Matsumoto, Y.; Mita, K.; Hashimoto, K.; Lio, H.; Tokoroyama, T. *Tetrahedron* **1996**, *52*, 9387, and references cited therein.

56. Sekar, G. Ph. D. Thesis, I. I. T. Kanpur.

57. Anand, R. V.; Pandey, G.; Singh, V. K. *Tetrahedron Lett*, **2002**, *43*, 3975.

58. For a review see: Chesney, A. *Green Chemistry* **1999**, 209.

59. For reviews on solid phase organic synthesis see: a) Thompson, L. A.; Ellman, J. A. *Chem. Rev.* **1996**, *96*, 555. b) Gordon, E. M.; Gallop, M. A.; Patel, D. V. *Acc. Chem. Res.* **1996**, *29*, 144.

60. For reviews on modified polymers, see: a) Bailey, D. C.; Langer, S. H. *Chem. Rev.* **1981**, *81*, 109. b) Akalah, A.; Sherrington, D. C. *Chem. Rev.* **1981**, *81*, 557. c) Sherrington, D. C.; Hodge, P. *Synthesis and Separation Using Functional Polymers*: Wiley, Chichester, 1988. d) Shuttleworth, S. J.; Allen, S. M.; Sharma, P. K. *Synthesis* **1997**, 1217.

61. a) For a review of the applications of cationic ion-exchange resins in this context, see: Chakrabarti, V.; Sharma, M. M. *React. Polym.* **1993**, *20*, 1. b) For a review of applications of anionic exchange resin supported reagents in organic synthesis, see: Kirchning, A.; Monenschein, H.; Witenberg, R. *Angew. Chem., Int. Ed. Engl.* **2001**, *40*, 650 and references therein.

62. a) Dockx, J. *Synthesis* **1973**, 441. b) Dehmlow, E. V. *Angew. Chem., Int. Ed. Engl.* **1974**, *13*, 170. c) Dehmlow, E. V.: Dehmlow, S. S. *Phase Transfer Catalysis*; 3rd Ed.; VCH: Weinheim, 1993.

63. a) Regen, S. L. *J. Am. Chem. Soc.* **1975**, *97*, 5956. b) Regen, S. L. *J. Am. Chem. Soc.* **1976**, *98*, 6270. c) Regen, S. L. *Catalysis in Organic Synthesis*; Academic Press, New York, 1977, pp. 119. d) Regen, S. L.; Nigam, A. *J. Am. Chem. Soc.* **1978**, *100*, 7773. e) Regen, S. L.; Lee, D. P. *J. Am. Chem. Soc.* **1974**, *96*, 294.

64. a) Regen, S. L.; Bolikal, D.; Barcelon, C. *J. Org. Chem.* **1981**, *46*, 2511. b) Molinari, H.; Montanari, F.; Quici, S.; Tundo, P. *J. Am. Chem. Soc.* **1979**, *101*, 3920.

65. a) Feinberg, R. S.; Merrifield, R. B. *Tetrahedron* **1974**, *30*, 3209. b) Stewart, J. M.; Jong, D. *Solid Phase PeptideSynthesis*; W. H. Freeman, San Francisco, California, 1969, pp. 56.

66. Regen, S. L. *J. Org. Chem.* **1977**, *42*, 875.

67. Komeili-Zadeh, H.; Dou, H. J. –M.; Metzger, J. *J. Org. Chem.* **1978**, *43*, 156.

68. Jacobson, S. E.; Mares, F.; Zambri, P. M. *J. Am. Chem. Soc.* **1979**, *101*, 6946.

69. House, H. O. *J. Am. Chem. Soc.* **1956**, *78*, 2298.

70. Payne, G. B.; Deming, P. H.; Williams, P. H. *J. Org. chem.* **1961**, *26*, 659.

71. For asymmetric epoxidation of enones with chiral cinchona alkaloids as phase transfer catalysts, see: a) Arai, S.; Tsuge, H.; Oku, M.; Miura, M.; Shioiri, T. *Tetrahedron* **2002**, *58*, 1623. b) Lygo, B.; Wainwright, P. G. *Tetrahedron* **1999**, *55*, 6289, and references therein.

72. Kobayashi, N.; Iwai, K. *Makromol. Chem. Rapid. Commun.* **1981**, *2*, 105.

73. a) Julia, S.; Masana, J.; Vega, J. C. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 929. b) Banfi, S.; Colonna, S.; Molinari, H.; Julia, S.; Guixer, J. *Tetrahedron* **1984**, *24*, 5207.

74. Anand, R. V.; Singh, V. K. *Synlett* **2000**, 807.

75. a) Saraswathy, V, G.; Sankararaman, S. *J. Org. Chem.* **1994**, *59*, 4665. b) Kamitori, Y.; Hojo, M.; Masuda, R.; Kimura, T.; Yoshida, T. *J. Org. chem.* **1986**, *51*, 1427.

76. Yu, H. –B.; Zheng, X. –F.; Lin, Z. –M.; Hu, Q. –S.; Huang, W. –S.; Pu, L. *J. Org. Chem.* **1999**, *64*, 8149.

77. Arai, S.; Shirai, Y.; Ishida, T.; Shioiri, T. *Tetrahedron* **1999**, *55*, 6375.

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List of Publications:

1. "A ring closing metathesis based approach to (+)-diplodialide A."

   R. Vijaya Anand, S. Baktharaman and Vinod. K. Singh. (Submitted)

2. "Elaboration of a Baylis-Hillman adduct to (-)-acaterin and its diastereomer through ring closing metathesis."

   R. Vijaya anand, S. Baktharaman and Vinod K. Singh *Tetrahedron Letters* **2002,** *43*, 5393.

3. "Silica gel induced cleavage of aziridines by aromatic amines under solvent free conditions"

   R. Vijaya Anand, Ghanshyam Pandey and Vinod K. Singh *Tetrahedron Letters*, **2002,** *43*, 3975.

4. "Triphase catalysis in epoxidation of α,β-enones with polymer bound quaternary ammonium salt"

   R. Vijaya Anand and Vinod K. Singh *Synlett*, **2000,** *6*, 807.

5. "Solvent free thioacetalization of carbonyl compounds catalyzed by $Cu(OTf)_2$-SiO_2"

   R. Vijaya Anand, P. Saravanan and Vinod K. Singh *Synlett*, **1999**, 415.

6. "$Cu(OTf)_2$ catalyzed trimethylsilyl cyanide addition to carbonyl compounds"

   P. Saravanan, **R. Vijaya Anand** and Vinod K. Singh *Tetrahedron Letters*, **1998**, *39*, 3823.

7. "An efficient method for deprotection of acetals"

P. Saravanan, M. Chandrasekhar, **R. Vijaya Anand** and Vinod K. Singh *Tetrahedron Letters*, **1998**, *39*, 3091.

8. "The unusual behavior of substituted 1-aryl-2-(arylamino)ethanones towards Vilsmeier reagent"

V. J. Majo, **R. Vijaya Anand** and P. T. Perumal, *Indian Journal of Chemistry*, **1999**, *38B*, 763.